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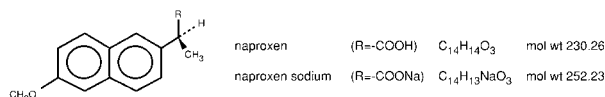
- EC-NAPROSYN[®] (naproxen delayed-release tablets)**
- NAPROSYN[®] (naproxen tablets)**
- ANAPROX[®]/ANAPROX[®] DS (naproxen sodium tablets)**
- NAPROSYN[®] (naproxen suspension)**

R_x only

DESCRIPTION

Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical names for naproxen and naproxen sodium are (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid and (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid, sodium salt, respectively. Naproxen and naproxen sodium have the following structures, respectively:



Naproxen has a molecular weight of 230.26 and a molecular formula of C₁₄H₁₄O₃. Naproxen sodium has a molecular weight of 252.23 and a molecular formula of C₁₄H₁₃NaO₃.

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

NAPROSYN (naproxen tablets) is available as yellow tablets containing 250 mg of naproxen, peach tablets containing 375 mg of naproxen and yellow tablets containing 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, iron oxides, povidone and magnesium stearate.

EC-NAPROSYN (naproxen delayed-release tablets) is available as enteric-coated white tablets containing 375 mg of naproxen and 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, povidone and magnesium stearate. The enteric coating dispersion contains methacrylic acid copolymer, talc, triethyl citrate, sodium hydroxide and purified water. The dispersion may also contain simethicone emulsion. The dissolution of this enteric-coated naproxen tablet is pH dependent with rapid dissolution above pH 6. There is no dissolution below pH 4.

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets), NAPROSYN® (naproxen suspension)

36 ANAPROX (naproxen sodium tablets) is available as blue tablets containing 275 mg of
37 naproxen sodium and ANAPROX DS (naproxen sodium tablets) is available as dark blue
38 tablets containing 550 mg of naproxen sodium for oral administration. The inactive
39 ingredients are magnesium stearate, microcrystalline cellulose, povidone and talc. The
40 coating suspension for the ANAPROX 275 mg tablet may contain hydroxypropyl
41 methylcellulose 2910, Opaspray K-1-4210A, polyethylene glycol 8000 or Opadry YS-1-
42 4215. The coating suspension for the ANAPROX DS 550 mg tablet may contain
43 hydroxypropyl methylcellulose 2910, Opaspray K-1-4227, polyethylene glycol 8000 or
44 Opadry YS-1-4216.

45 NAPROSYN (naproxen suspension) is available as a light orange-colored opaque oral
46 suspension containing 125 mg/5 mL of naproxen in a vehicle containing sucrose,
47 magnesium aluminum silicate, sorbitol solution and sodium chloride (30 mg/5 mL, 1.5
48 mEq), methylparaben, fumaric acid, FD&C Yellow No. 6, imitation pineapple flavor,
49 imitation orange flavor and purified water. The pH of the suspension ranges from 2.2 to
50 3.7.

51 **CLINICAL PHARMACOLOGY**

52 **Pharmacodynamics:** Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with
53 analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a
54 more rapidly absorbed formulation of naproxen for use as an analgesic. The mechanism
55 of action of the naproxen anion, like that of other NSAIDs, is not completely understood
56 but may be related to prostaglandin synthetase inhibition.

57 **Pharmacokinetics:** Naproxen itself is rapidly and completely absorbed from the
58 gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms
59 of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak
60 concentration (C_{max}); however, the products do differ in their pattern of absorption. These
61 differences between naproxen products are related to both the chemical form of naproxen
62 used and its formulation. Even with the observed differences in pattern of absorption, the
63 elimination half-life of naproxen is unchanged across products ranging from 12 to 17
64 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of
65 naproxen accumulation is consistent with this half-life. This suggests that the differences
66 in pattern of release play only a negligible role in the attainment of steady-state plasma
67 levels.

68 **Absorption:**

69 **Immediate Release:** After administration of NAPROSYN tablets, peak plasma levels are
70 attained in 2 to 4 hours. After oral administration of ANAPROX, peak plasma levels are
71 attained in 1 to 2 hours. The difference in rates between the two products is due to the
72 increased aqueous solubility of the sodium salt of naproxen used in ANAPROX. Peak
73 plasma levels of naproxen given as NAPROSYN Suspension are attained in 1 to 4 hours.

74 **Delayed Release:** EC-NAPROSYN is designed with a pH-sensitive coating to provide a
75 barrier to disintegration in the acidic environment of the stomach and to lose integrity in

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76 the more neutral environment of the small intestine. The enteric polymer coating selected
77 for EC-NAPROSYN dissolves above pH 6. When EC-NAPROSYN was given to fasted
78 subjects, peak plasma levels were attained about 4 to 6 hours following the first dose
79 (range: 2 to 12 hours). An in vivo study in man using radiolabeled EC-NAPROSYN
80 tablets demonstrated that EC-NAPROSYN dissolves primarily in the small intestine
81 rather than the stomach, so the absorption of the drug is delayed until the stomach is
82 emptied.

83 When EC-NAPROSYN and NAPROSYN were given to fasted subjects (n=24) in a
84 crossover study following 1 week of dosing, differences in time to peak plasma levels
85 (T_{max}) were observed, but there were no differences in total absorption as measured by
86 C_{max} and AUC:

	EC-NAPROSYN* 500 mg bid	NAPROSYN* 500 mg bid
C_{max} (µg/mL)	94.9 (18%)	97.4 (13%)
T_{max} (hours)	4 (39%)	1.9 (61%)
AUC _{0-12 hr} (µg·hr/mL)	845 (20%)	767 (15%)

87 *Mean value (coefficient of variation)

88 *Antacid Effects:* When EC-NAPROSYN was given as a single dose with antacid (54 mEq
89 buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to
90 peak was reduced (mean T_{max} fasted 5.6 hours, mean T_{max} with antacid 5 hours), although
91 not significantly.

92 *Food Effects:* When EC-NAPROSYN was given as a single dose with food, peak plasma
93 levels in most subjects were achieved in about 12 hours (range: 4 to 24 hours). Residence
94 time in the small intestine until disintegration was independent of food intake. The
95 presence of food prolonged the time the tablets remained in the stomach, time to first
96 detectable serum naproxen levels, and time to maximal naproxen levels (T_{max}), but did
97 not affect peak naproxen levels (C_{max}).

98 *Distribution:*

99 Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is
100 greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is
101 less than proportional increase in plasma levels due to an increase in clearance caused by
102 saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and
103 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen). The naproxen anion
104 has been found in the milk of lactating women at a concentrations equivalent to
105 approximately 1% of maximum naproxen concentration in plasma (see PRECAUTIONS:
106 *Nursing Mothers*).

107 *Metabolism:*

108 Naproxen is extensively metabolized to 6-O-desmethyl naproxen, and both parent and
109 metabolites do not induce metabolizing enzymes.

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110 **Excretion:**

111 The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from
112 any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl
113 naproxen (less than 1%) or their conjugates (66% to 92%). The plasma half-life of the
114 naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of
115 both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of
116 excretion have been found to coincide closely with the rate of naproxen disappearance
117 from the plasma. In patients with renal failure metabolites may accumulate (see
118 PRECAUTIONS: *Renal Effects*).

119 **Special Populations:**

120 *Pediatric Patients:* In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen
121 levels following a 5 mg/kg single dose of naproxen suspension (see DOSAGE AND
122 ADMINISTRATION) were found to be similar to those found in normal adults following
123 a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients.
124 Pharmacokinetic studies of naproxen were not performed in pediatric patients younger
125 than 5 years of age. Pharmacokinetic parameters appear to be similar following
126 administration of naproxen suspension or tablets in pediatric patients. EC-NAPROSYN
127 has not been studied in subjects under the age of 18.

128 *Geriatric Patients:* Studies indicate that although total plasma concentration of naproxen
129 is unchanged, the unbound plasma fraction of naproxen is increased in the elderly,
130 although the unbound fraction is less than 1% of the total naproxen concentration.
131 Unbound trough naproxen concentrations in elderly subjects have been reported to range
132 from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075%
133 in younger subjects. The clinical significance of this finding is unclear, although it is
134 possible that the increase in free naproxen concentration could be associated with an
135 increase in the rate of adverse events per a given dosage in some elderly patients.

136 *Race:* Pharmacokinetic differences due to race have not been studied.

137 *Hepatic Insufficiency:* Naproxen pharmacokinetics has not been determined in subjects
138 with hepatic insufficiency.

139 *Renal Insufficiency:* Naproxen pharmacokinetics has not been determined in subjects
140 with renal insufficiency. Given that naproxen, its metabolites and conjugates are
141 primarily excreted by the kidney, the potential exists for naproxen metabolites to
142 accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased
143 in patients with severe renal impairment. Naproxen-containing products are not
144 recommended for use in patients with moderate to severe and severe renal impairment
145 (creatinine < 30 ml/min) (see PRECAUTIONS: *Renal Effects*).

146 **CLINICAL STUDIES**

147 **General Information:** Naproxen has been studied in patients with rheumatoid arthritis,
148 osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute
149 gout. Improvement in patients treated for rheumatoid arthritis was demonstrated by a

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150 reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in
151 disease activity as assessed by both the investigator and patient, and by increased
152 mobility as demonstrated by a reduction in walking time. Generally, response to
153 naproxen has not been found to be dependent on age, sex, severity or duration of
154 rheumatoid arthritis.

155 In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a
156 reduction in joint pain or tenderness, an increase in range of motion in knee joints,
157 increased mobility as demonstrated by a reduction in walking time, and improvement in
158 capacity to perform activities of daily living impaired by the disease.

159 In a clinical trial comparing standard formulations of naproxen 375 mg bid (750 mg a
160 day) vs 750 mg bid (1500 mg/day), 9 patients in the 750 mg group terminated
161 prematurely because of adverse events. Nineteen patients in the 1500 mg group
162 terminated prematurely because of adverse events. Most of these adverse events were
163 gastrointestinal events.

164 In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile
165 arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in
166 controlling the aforementioned measures of disease activity, but the frequency and
167 severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and
168 nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in
169 naproxen-treated patients than in those treated with aspirin or indomethacin.

170 In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain,
171 morning stiffness and pain at rest. In double-blind studies the drug was shown to be as
172 effective as aspirin, but with fewer side effects.

173 In patients with acute gout, a favorable response to naproxen was shown by significant
174 clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24 to 48 hours,
175 as well as by relief of pain and tenderness.

176 Naproxen has been studied in patients with mild to moderate pain secondary to
177 postoperative, orthopedic, postpartum episiotomy and uterine contraction pain and
178 dysmenorrhea. Onset of pain relief can begin within 1 hour in patients taking naproxen
179 and within 30 minutes in patients taking naproxen sodium. Analgesic effect was shown
180 by such measures as reduction of pain intensity scores, increase in pain relief scores,
181 decrease in numbers of patients requiring additional analgesic medication, and delay in
182 time to remedication. The analgesic effect has been found to last for up to 12 hours.

183 Naproxen may be used safely in combination with gold salts and/or corticosteroids;
184 however, in controlled clinical trials, when added to the regimen of patients receiving
185 corticosteroids, it did not appear to cause greater improvement over that seen with
186 corticosteroids alone. Whether naproxen has a “steroid-sparing” effect has not been
187 adequately studied. When added to the regimen of patients receiving gold salts, naproxen
188 did result in greater improvement. Its use in combination with salicylates is not
189 recommended because there is evidence that aspirin increases the rate of excretion of

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190 naproxen and data are inadequate to demonstrate that naproxen and aspirin produce
191 greater improvement over that achieved with aspirin alone. In addition, as with other
192 NSAIDs, the combination may result in higher frequency of adverse events than
193 demonstrated for either product alone.

194 In ⁵¹Cr blood loss and gastroscopy studies with normal volunteers, daily administration of
195 1000 mg of naproxen as 1000 mg of NAPROSYN (naproxen) or 1100 mg of ANAPROX
196 (naproxen sodium) has been demonstrated to cause statistically significantly less gastric
197 bleeding and erosion than 3250 mg of aspirin.

198 Three 6-week, double-blind, multicenter studies with EC-NAPROSYN (naproxen) (375
199 or 500 mg bid, n=385) and NAPROSYN (375 or 500 mg bid, n=279) were conducted
200 comparing EC-NAPROSYN with NAPROSYN, including 355 rheumatoid arthritis and
201 osteoarthritis patients who had a recent history of NSAID-related GI symptoms. These
202 studies indicated that EC-NAPROSYN and NAPROSYN showed no significant
203 differences in efficacy or safety and had similar prevalence of minor GI complaints.
204 Individual patients, however, may find one formulation preferable to the other.

205 Five hundred and fifty-three patients received EC-NAPROSYN during long-term open-
206 label trials (mean length of treatment was 159 days). The rates for clinically-diagnosed
207 peptic ulcers and GI bleeds were similar to what has been historically reported for long-
208 term NSAID use.

209 **Geriatric Patients:** The hepatic and renal tolerability of long-term naproxen
210 administration was studied in two double blind clinical trials involving 586 patients. Of
211 the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age
212 75 and older. Naproxen was administered at doses of 375 mg twice daily or 750 mg twice
213 daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and
214 renal function were noted in some patients, although there were no differences noted in
215 the occurrence of abnormal values among different age groups.

216 **INDIVIDUALIZATION OF DOSAGE**

217 Although NAPROSYN, NAPROSYN Suspension, EC-NAPROSYN, ANAPROX and
218 ANAPROX DS all circulate in the plasma as naproxen, they have pharmacokinetic
219 differences that may affect onset of action. Onset of pain relief can begin within 30
220 minutes in patients taking naproxen sodium and within 1 hour in patients taking
221 naproxen. Because EC-NAPROSYN dissolves in the small intestine rather than in the
222 stomach, the absorption of the drug is delayed compared to the other naproxen
223 formulations (see CLINICAL PHARMACOLOGY).

224 The recommended strategy for initiating therapy is to choose a formulation and a starting
225 dose likely to be effective for the patient and then adjust the dosage based on observation
226 of benefit and/or adverse events. A lower dose should be considered in patients with renal
227 or hepatic impairment or in elderly patients (see PRECAUTIONS).

228 **Analgesia/Dysmenorrhea/Bursitis and Tendinitis:** Because the sodium salt of naproxen
229 is more rapidly absorbed, ANAPROX/ANAPROX DS is recommended for the

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230 management of acute painful conditions when prompt onset of pain relief is desired. The
231 recommended starting dose is 550 mg followed by 550 mg every 12 hours or 275 mg
232 every 6 to 8 hours, as required. The initial total daily dose should not exceed 1375 mg of
233 naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen
234 sodium. NAPROSYN may also be used for treatment of acute pain and dysmenorrhea.
235 EC-NAPROSYN is not recommended for initial treatment of acute pain because
236 absorption of naproxen is delayed compared to other naproxen-containing products (see
237 CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE).

238 **Acute Gout:** The recommended starting dose is 750 mg of NAPROSYN followed by 250
239 mg every 8 hours until the attack has subsided. ANAPROX may also be used at a starting
240 dose of 825 mg followed by 275 mg every 8 hours as needed. EC-NAPROSYN is not
241 recommended because of the delay in absorption (see CLINICAL PHARMACOLOGY).

242 **Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis:** The recommended dose of
243 naproxen is NAPROSYN or NAPROSYN Suspension 250 mg, 375 mg or 500 mg taken
244 twice daily (morning and evening) or EC-NAPROSYN 375 mg or 500 mg taken twice
245 daily. Naproxen sodium may also be used (see DOSAGE AND ADMINISTRATION).

246 During long-term administration the dose of naproxen may be adjusted up or down
247 depending on the clinical response of the patient. A lower daily dose may suffice for
248 long-term administration. In patients who tolerate lower doses well, the dose may be
249 increased to 1500 mg per day for up to 6 months when a higher level of anti-
250 inflammatory/analgesic activity is required. When treating patients with naproxen 1500
251 mg/day (as NAPROSYN or 1650 mg of ANAPROX), the physician should observe
252 sufficient increased clinical benefit to offset the potential increased risk. The morning and
253 evening doses do not have to be equal in size and administration of the drug more
254 frequently than twice daily does not generally make a difference in response (see
255 CLINICAL PHARMACOLOGY).

256 **Juvenile Arthritis:** The use of NAPROSYN Suspension allows for more flexible dose
257 titration. In pediatric patients, doses of 5 mg/kg/day produced plasma levels of naproxen
258 similar to those seen in adults taking 500 mg of naproxen (see CLINICAL
259 PHARMACOLOGY).

260 The recommended total daily dose is approximately 10 mg/kg given in two divided doses
261 (ie, 5 mg/kg given twice a day) (see DOSAGE AND ADMINISTRATION).

262 **INDICATIONS AND USAGE**

263 Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or
264 NAPROSYN Suspension is indicated:

- 265 • For the relief of the signs and symptoms of rheumatoid arthritis
- 266 • For the relief of the signs and symptoms of osteoarthritis
- 267 • For the relief of the signs and symptoms of ankylosing spondylitis

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- 268 • For the relief of the signs and symptoms of juvenile arthritis
- 269 Naproxen as NAPROSYN Suspension is recommended for juvenile rheumatoid arthritis
270 in order to obtain the maximum dosage flexibility based on the patient’s weight.
- 271 Naproxen as NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension is
272 also indicated:
- 273 • For relief of the signs and symptoms of tendinitis
- 274 • For relief of the signs and symptoms of bursitis
- 275 • For relief of the signs and symptoms of acute gout
- 276 • For the management of pain
- 277 • For the management of primary dysmenorrhea
- 278 EC-NAPROSYN is not recommended for initial treatment of acute pain because the
279 absorption of naproxen is delayed compared to absorption from other naproxen-
280 containing products (see CLINICAL PHARMACOLOGY and DOSAGE AND
281 ADMINISTRATION).

282 **CONTRAINDICATIONS**

283 All naproxen products are contraindicated in patients who have had allergic reactions to
284 prescription as well as to over-the-counter products containing naproxen. It is also
285 contraindicated in patients in whom aspirin or other nonsteroidal anti-
286 inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps.
287 Both types of reactions have the potential of being fatal. Anaphylactoid reactions to
288 naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (eg, aspirin
289 hypersensitivity syndrome) type, usually but not always occur in patients with a known
290 history of such reactions. Therefore, careful questioning of patients for such things as
291 asthma, nasal polyps, urticaria, and hypotension associated with nonsteroidal anti-
292 inflammatory drugs before starting therapy is important. In addition, if such symptoms
293 occur during therapy, treatment should be discontinued (see WARNINGS: *Anaphylactoid*
294 *Reactions* and PRECAUTIONS: *Preexisting Asthma*).

295 **WARNINGS**

296 ***Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation:***
297 Serious gastrointestinal toxicity such as bleeding, ulceration and perforation of the
298 stomach, small intestine or large intestine, can occur at any time, with or without warning
299 symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs).
300 Minor upper gastrointestinal problems, such as dyspepsia, are common and may also
301 occur at any time during NSAID therapy. Therefore, physicians and patients should
302 remain alert for ulceration and bleeding, even in the absence of previous GI tract
303 symptoms (see PRECAUTIONS: *Hematological Effects*). Patients should be informed
304 about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur.

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305 The utility of periodic laboratory monitoring has not been demonstrated, nor has it been
306 adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event
307 on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross
308 bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of
309 patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year.
310 These trends continue, thus increasing the likelihood of developing a serious GI event at
311 some time during the course of therapy. However, even short-term therapy is not without
312 risk.

313 NSAIDs should be prescribed with extreme caution in patients with a prior history of
314 ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are
315 in elderly or debilitated patients and therefore special care should be taken in treating this
316 population. **To minimize the potential risk for an adverse GI event, the lowest
317 effective dose should be used for the shortest possible duration.** For high-risk patients,
318 alternate therapies that do not involve NSAIDs should be considered.

319 Studies have shown that patients with a *prior history of peptic ulcer disease and/or*
320 *gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for
321 developing a GI bleed than patients with neither of these risk factors. In addition to a past
322 history of ulcer disease, pharmacoepidemiological studies have identified several other
323 co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as:
324 treatment with oral corticosteroids, treatment with anticoagulants, longer duration of
325 NSAID therapy, smoking, alcoholism, older age, and poor general health status.

326 **Anaphylactoid Reactions:** As with other NSAIDs, anaphylactoid reactions may occur in
327 patients without known prior exposure to naproxen. Naproxen should not be given to
328 patients with the aspirin triad. This symptom complex typically occurs in asthmatic
329 patients who experience rhinitis with or without nasal polyps, or who exhibit severe,
330 potentially fatal bronchospasm after taking aspirin or other NSAIDs (see
331 CONTRAINDICATIONS and PRECAUTIONS: *Preexisting Asthma*). Emergency help
332 should be sought in cases where an anaphylactoid reaction occurs.

333 **Advanced Renal Disease:** In cases with advanced kidney disease, treatment with
334 naproxen is not recommended. If NSAID therapy, however, must be initiated, close
335 monitoring of the patient's kidney function is advisable (see PRECAUTIONS: *Renal*
336 *Effects*).

337 **Pregnancy:** In late pregnancy, as with other NSAIDs, naproxen should be avoided
338 because it may cause premature closure of the ductus arteriosus.

339 **PRECAUTIONS**

340 **General:** NAPROXEN-CONTAINING PRODUCTS SUCH AS NAPROSYN, EC-
341 NAPROSYN, ANAPROX, ANAPROX DS, NAPROSYN SUSPENSION, ALEVE®*,
342 AND OTHER NAPROXEN PRODUCTS SHOULD NOT BE USED
343 CONCOMITANTLY SINCE THEY ALL CIRCULATE IN THE PLASMA AS
344 THE NAPROXEN ANION.

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345 Naproxen cannot be expected to substitute for corticosteroids or to treat corticosteroid
346 insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation.
347 Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a
348 decision is made to discontinue corticosteroids and the patient should be observed closely
349 for any evidence of adverse effects, including adrenal insufficiency and exacerbation of
350 symptoms of arthritis.

351 Patients with initial hemoglobin values of 10 g or less who are to receive long-term
352 therapy should have hemoglobin values determined periodically.

353 The antipyretic and anti-inflammatory activities of the drug may reduce fever and
354 inflammation, thus diminishing their utility as diagnostic signs in detecting complications
355 of presumed noninfectious, noninflammatory painful conditions.

356 Because of adverse eye findings in animal studies with drugs of this class, it is
357 recommended that ophthalmic studies be carried out if any change or disturbance in
358 vision occurs.

359 **Hepatic Effects:** As with other nonsteroidal anti-inflammatory drugs, borderline
360 elevations of one or more liver tests may occur in up to 15% of patients. These
361 abnormalities may progress, may remain essentially unchanged, or may be transient with
362 continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver
363 dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or
364 SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient
365 with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver
366 test has occurred, should be evaluated for evidence of the development of more severe
367 hepatic reaction while on therapy with naproxen. Severe hepatic reactions, including
368 jaundice and cases of fatal hepatitis, have been reported with naproxen as with other
369 nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver
370 tests persist or worsen, if clinical signs and symptoms consistent with liver disease
371 develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), naproxen
372 should be discontinued.

373 **Renal Effects:** Caution should be used when initiating treatment with naproxen in
374 patients with considerable dehydration. It is advisable to rehydrate patients first and then
375 start therapy with naproxen. Caution is also recommended in patients with pre-existing
376 kidney disease (see WARNINGS: *Advanced Renal Disease*).

377 As with other nonsteroidal anti-inflammatory drugs, long-term administration of
378 naproxen to animals has resulted in renal papillary necrosis and other abnormal renal
379 pathology. In humans, there have been reports of impaired renal function, renal failure,
380 acute interstitial nephritis, hematuria, proteinuria, renal papillary necrosis, and
381 occasionally nephrotic syndrome associated with naproxen-containing products and other
382 NSAIDs since they have been marketed.

383 A second form of renal toxicity has been seen in patients taking naproxen as well as other
384 nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to a

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385 reduction in renal blood flow or blood volume, where the renal prostaglandins have a
386 supportive role in the maintenance of renal perfusion, caution should be observed since
387 administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent
388 reduction in prostaglandin formation and may precipitate overt renal decompensation or
389 failure. Patients at greatest risk of this reaction are those with impaired renal function,
390 hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and
391 ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory
392 therapy is typically followed by recovery to the pretreatment state.

393 Naproxen and its metabolites are eliminated primarily by the kidneys; therefore, the drug
394 should be used with caution in such patients and the monitoring of serum creatinine
395 and/or creatinine clearance is advised. A reduction in daily dosage should be considered
396 to avoid the possibility of excessive accumulation of naproxen metabolites in these
397 patients. Naproxen-containing products are not recommended for use in patients with
398 moderate to severe and severe renal impairment (creatinine < 30 ml/min).

399 Chronic alcoholic liver disease and probably other diseases with decreased or abnormal
400 plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the
401 plasma concentration of unbound naproxen is increased. Caution is advised when high
402 doses are required and some adjustment of dosage may be required in these patients. It is
403 prudent to use the lowest effective dose.

404 Studies indicate that although total plasma concentration of naproxen is unchanged, the
405 unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when
406 high doses are required and some adjustment of dosage may be required in elderly
407 patients. As with other drugs used in the elderly, it is prudent to use the lowest effective
408 dose.

409 **Hematological Effects:** Anemia is sometimes seen in patients receiving NSAIDs,
410 including naproxen. This may be due to fluid retention, GI loss, or an incompletely
411 described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs,
412 including naproxen, should have their hemoglobin or hematocrit checked if they exhibit
413 any signs or symptoms of anemia.

414 All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent
415 with platelet function and vascular responses to bleeding.

416 NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in
417 some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of
418 shorter duration, and reversible. Naproxen does not generally affect platelet counts,
419 prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving naproxen
420 who may be adversely affected by alterations in platelet function, such as those with
421 coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

422 **Fluid Retention and Edema:** Peripheral edema has been observed in some patients
423 receiving naproxen. Since each ANAPROX or ANAPROX DS tablet contains 25 mg or
424 50 mg of sodium (about 1 mEq per each 250 mg of naproxen), and each teaspoonful of

EC-NAPROSYN[®] (naproxen delayed-release tablets), NAPROSYN[®] (naproxen tablets), ANAPROX[®]/ANAPROX[®] DS (naproxen sodium tablets), NAPROSYN[®] (naproxen suspension)

425 NAPROSYN Suspension contains 39 mg (about 1.5 mEq per each 125 mg of naproxen)
426 of sodium, this should be considered in patients whose overall intake of sodium must be
427 severely restricted. For these reasons, ANAPROX, ANAPROX DS and NAPROSYN
428 Suspension should be used with caution in patients with fluid retention, hypertension or
429 heart failure.

430 ***Preexisting Asthma:*** Patients with asthma may have aspirin-sensitive asthma. The use of
431 aspirin in patients with aspirin-sensitive asthma has been associated with severe
432 bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm,
433 between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such
434 aspirin-sensitive patients, naproxen should not be administered to patients with this form
435 of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

436 ***Information for Patients:*** Naproxen, in NAPROSYN, EC-NAPROSYN, ANAPROX,
437 ANAPROX DS and NAPROSYN Suspension can cause discomfort and, rarely, more
438 serious side effects, such as gastrointestinal bleeding, which may result in hospitalization
439 and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur
440 without warning symptoms, patients should be alert for the signs and symptoms of
441 ulcerations and bleeding, and should ask for medical advice when observing any
442 indicative signs or symptoms. Patients should be apprised of the importance of this
443 follow-up (see WARNINGS: *Gastrointestinal (GI) Effects-Risk of GI Ulceration,*
444 *Bleeding, and Perforation*).

445 Patients should promptly report signs or symptoms of gastrointestinal ulceration or
446 bleeding, skin rash, unexplained weight gain or edema to their physicians.

447 Patients should be informed of the warning signs and symptoms of hepatotoxicity (eg,
448 nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-
449 like” symptoms). If these occur, patients should be instructed to stop therapy and seek
450 immediate medical therapy.

451 Patients should also be instructed to seek immediate emergency help in the case of an
452 anaphylactoid reaction (see WARNINGS).

453 In late pregnancy, naproxen, in NAPROSYN, EC-NAPROSYN, ANAPROX,
454 ANAPROX DS, and NAPROSYN SUSPENSION, should be avoided because it may
455 cause premature closure of the ductus arteriosus.

456 Caution should be exercised by patients whose activities require alertness if they
457 experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.

458 ***Laboratory Tests:*** Because serious GI tract ulcerations and bleeding can occur without
459 warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. If
460 clinical signs and symptoms consistent with liver or renal disease develop, systemic
461 manifestations occur (eg, eosinophilia, rash, etc.) or if abnormal liver tests persist or
462 worsen, naproxen should be discontinued.

463 ***Drug Interactions:***

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464 *Aspirin:* Concomitant administration of naproxen and aspirin is not recommended
465 because naproxen is displaced from its binding sites during the concomitant
466 administration of aspirin, resulting in lower plasma concentrations and peak plasma
467 levels.

468 *Methotrexate:* Caution should be used if naproxen is administered concomitantly with
469 methotrexate. Naproxen, naproxen sodium and other nonsteroidal anti-inflammatory
470 drugs have been reported to reduce the tubular secretion of methotrexate in an animal
471 model, possibly increasing the toxicity of methotrexate.

472 *ACE-inhibitors:* Reports suggest that NSAIDs may diminish the antihypertensive effect
473 of ACE-inhibitors. The use of NSAIDs in patients who are receiving ACE inhibitors may
474 potentiate renal disease states (see PRECAUTIONS: *Renal Effects*).

475 *Furosemide:* Clinical studies, as well as postmarketing observations, have shown that
476 NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients.
477 This response has been attributed to inhibition of renal prostaglandin synthesis.

478 *Lithium:* Inhibition of renal lithium clearance leading to increases in plasma lithium
479 concentrations has also been reported. The mean minimum lithium concentration
480 increased 15% and the renal clearance was decreased by approximately 20%. These
481 effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID.
482 Thus, when NSAIDs and lithium are administered concurrently, patients should be
483 observed carefully for signs of lithium toxicity.

484 *Warfarin:* The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that
485 patients taking both drugs have a risk of serious GI bleeding that is higher than patients
486 taking either drug alone. No significant interactions have been observed in clinical
487 studies with naproxen and coumarin-type anticoagulants. However, caution is advised
488 since interactions have been seen with other nonsteroidal agents of this class. The free
489 fraction of warfarin may increase substantially in some subjects and naproxen interferes
490 with platelet function.

491 ***Other Information Concerning Drug Interactions:***

492 Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for
493 interaction with other albumin-bound drugs such as coumarin-type anticoagulants,
494 sulphonylureas, hydantoin, other NSAIDs, and aspirin. Patients simultaneously
495 receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed
496 for adjustment of dose if required.

497 Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the
498 antihypertensive effect of propranolol and other beta-blockers.

499 Probenecid given concurrently increases naproxen anion plasma levels and extends its
500 plasma half-life significantly.

501 Due to the gastric pH elevating effects of H₂-blockers, sucralfate and intensive antacid
502 therapy, concomitant administration of EC-NAPROSYN is not recommended.

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503 ***Drug/Laboratory Test Interactions:*** Naproxen may decrease platelet aggregation and
504 prolong bleeding time. This effect should be kept in mind when bleeding times are
505 determined.

506 The administration of naproxen may result in increased urinary values for 17-ketogenic
507 steroids because of an interaction between the drug and/or its metabolites with m-di-
508 nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements
509 (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy
510 with naproxen be temporarily discontinued 72 hours before adrenal function tests are
511 performed if the Porter-Silber test is to be used.

512 Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid
513 (5HIAA).

514 ***Carcinogenesis:*** A 2-year study was performed in rats to evaluate the carcinogenic
515 potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/m²).
516 The maximum dose used was 0.28 times the systemic exposure to humans at the
517 recommended dose. No evidence of tumorigenicity was found.

518 ***Pregnancy: Teratogenic Effects:*** Pregnancy Category C. Reproduction studies have been
519 performed in rats at 20 mg/kg/day (125 mg/m²/day, 0.23 times the human systemic
520 exposure), rabbits at 20 mg/kg/day (220 mg/m²/day, 0.27 times the human systemic
521 exposure), and mice at 170 mg/kg/day (510 mg/m²/day, 0.28 times the human systemic
522 exposure) with no evidence of impaired fertility or harm to the fetus due to the drug.
523 There are no adequate and well-controlled studies in pregnant women. Because animal
524 reproduction studies are not always predictive of human response, naproxen should not
525 be used during pregnancy unless clearly needed.

526 ***Nonteratogenic Effects:*** There is some evidence to suggest that when inhibitors of
527 prostaglandin synthesis are used to delay preterm labor there is an increased risk of
528 neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and
529 intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition
530 has been associated with persistent pulmonary hypertension, renal dysfunction and
531 abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs
532 of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use
533 during third trimester should be avoided.

534 ***Labor and Delivery:*** In rat studies with NSAIDs, as with other drugs known to inhibit
535 prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and
536 decreased pup survival occurred. Naproxen-containing products are not recommended in
537 labor and delivery because, through its prostaglandin synthesis inhibitory effect,
538 naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus
539 increasing the risk of uterine hemorrhage.

540 ***Nursing Mothers:*** The naproxen anion has been found in the milk of lactating women at
541 a concentrations equivalent to approximately 1% of maximum naproxen concentration in

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542 plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on
543 neonates, use in nursing mothers should be avoided.

544 ***Pediatric Use:*** Safety and effectiveness in pediatric patients below the age of 2 years
545 have not been established. Pediatric dosing recommendations for juvenile arthritis are
546 based on well-controlled studies (see DOSAGE AND ADMINISTRATION). There are
547 no adequate effectiveness or dose-response data for other pediatric conditions, but the
548 experience in juvenile arthritis and other use experience have established that single
549 doses of 2.5 to 5 mg/kg (as naproxen suspension, see DOSAGE AND
550 ADMINISTRATION), with total daily dose not exceeding 15 mg/kg/day, are well
551 tolerated in pediatric patients over 2 years of age.

552 ***Geriatric Use:*** Studies indicate that although total plasma concentration of naproxen is
553 unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution
554 is advised when high doses are required and some adjustment of dosage may be required
555 in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest
556 effective dose.

557 Experience indicates that geriatric patients may be particularly sensitive to certain
558 adverse effects of nonsteroidal anti-inflammatory drugs. While age does not appear to be
559 an independent risk factor for the development of peptic ulceration and bleeding with
560 naproxen administration, elderly or debilitated patients seem to tolerate peptic ulceration
561 or bleeding less well when these events do occur. Most spontaneous reports of fatal GI
562 events are in the geriatric population (see WARNINGS).

563 Naproxen is known to be substantially excreted by the kidney, and the risk of toxic
564 reactions to this drug may be greater in patients with impaired renal function. Because
565 elderly patients are more likely to have decreased renal function, care should be taken in
566 dose selection, and it may be useful to monitor renal function. Geriatric patients may be
567 at a greater risk for the development of a form of renal toxicity precipitated by reduced
568 prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs
569 (see PRECAUTIONS: *Renal Effects*).

570 **ADVERSE REACTIONS**

571 Adverse reactions reported in controlled clinical trials in 960 patients treated for
572 rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients
573 treated chronically were reported 2 to 10 times more frequently than they were in short-
574 term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea.
575 The most frequent complaints reported related to the gastrointestinal tract.

576 A clinical study found gastrointestinal reactions to be more frequent and more severe in
577 rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those
578 taking 750 mg naproxen (see CLINICAL PHARMACOLOGY).

579 In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-
580 label studies with about 400 pediatric patients with juvenile arthritis treated with
581 naproxen, the incidence of rash and prolonged bleeding times were increased, the

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582 incidence of gastrointestinal and central nervous system reactions were about the same,
583 and the incidence of other reactions were lower in pediatric patients than in adults.

584 In patients taking naproxen in clinical trials, the most frequently reported adverse
585 experiences in approximately 1 to 10% of patients are:

586 **Gastrointestinal (GI) Experiences, including:** heartburn*, abdominal pain*, nausea*,
587 constipation*, diarrhea, dyspepsia, stomatitis

588 **Central Nervous System:** headache*, dizziness*, drowsiness*, lightheadedness, vertigo

589 **Dermatologic:** pruritus (itching) *, skin eruptions*, ecchymoses*, sweating, purpura

590 **Special Senses:** tinnitus*, visual disturbances, hearing disturbances

591 **Cardiovascular:** edema*, palpitations

592 **General:** dyspnea*, thirst

593 * Incidence of reported reaction between 3% and 9%. Those reactions occurring in less
594 than 3% of the patients are unmarked.

595 In patients taking NSAIDs, the following adverse experiences have also been reported in
596 approximately 1 to 10% of patients.

597 **Gastrointestinal (GI) Experiences, including:** flatulence, gross bleeding/perforation, GI
598 ulcers (gastric/duodenal), vomiting

599 **General:** abnormal renal function, anemia, elevated liver enzymes, increased bleeding
600 time, rashes

601 The following are additional adverse experiences reported in <1% of patients taking
602 naproxen during clinical trials and through post-marketing reports. Those adverse
603 reactions observed through post-marketing reports are italicized.

604 **Body as a Whole:** *anaphylactoid reactions, angioneurotic edema, menstrual disorders,*
605 *pyrexia (chills and fever)*

606 **Cardiovascular:** *congestive heart failure, vasculitis*

607 **Gastrointestinal:** *gastrointestinal bleeding and/or perforation, hematemesis, jaundice,*
608 *pancreatitis, vomiting, colitis, abnormal liver function tests, nonpeptic gastrointestinal*
609 *ulceration, ulcerative stomatitis*

610 **Hemic and Lymphatic:** *eosinophilia, leucopenia, melena, thrombocytopenia,*
611 *agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia*

612 **Metabolic and Nutritional:** *hyperglycemia, hypoglycemia*

613 **Nervous System:** *inability to concentrate, depression, dream abnormalities, insomnia,*
614 *malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction*

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615 **Respiratory:** *eosinophilic pneumonitis*

616 **Dermatologic:** *alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema*
617 *multiforme, Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity*
618 *reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria)*
619 *or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of*
620 *pseudoporphyria occur, treatment should be discontinued and the patient monitored.*

621 **Special Senses:** *hearing impairment*

622 **Urogenital:** *glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis,*
623 *nephrotic syndrome, renal disease, renal failure, renal papillary necrosis*

624 In patients taking NSAIDs, the following adverse experiences have also been reported in
625 <1% of patients.

626 **Body as a Whole:** fever, infection, sepsis, anaphylactic reactions, appetite changes, death

627 **Cardiovascular:** hypertension, tachycardia, syncope, arrhythmia, hypotension,
628 myocardial infarction

629 **Gastrointestinal:** dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis,
630 hepatitis, eructation, liver failure

631 **Hemic and Lymphatic:** rectal bleeding, lymphadenopathy, pancytopenia

632 **Metabolic and Nutritional:** weight changes

633 **Nervous System:** anxiety, asthenia, confusion, nervousness, paresthesia, somnolence,
634 tremors, convulsions, coma, hallucinations

635 **Respiratory:** asthma, respiratory depression, pneumonia

636 **Dermatologic:** exfoliative dermatitis

637 **Special Senses:** blurred vision, conjunctivitis

638 **Urogenital:** cystitis, dysuria, oliguria/polyuria, proteinuria

639 **OVERDOSAGE**

640 Significant naproxen overdose may be characterized by lethargy, dizziness,
641 drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea,
642 transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic
643 acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur.
644 Hypertension, acute renal failure, respiratory depression, and coma may occur, but are
645 rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs,
646 and may occur following an overdose. Because naproxen sodium may be rapidly
647 absorbed, high and early blood levels should be anticipated. A few patients have
648 experienced convulsions, but it is not clear whether or not these were drug-related. It is
649 not known what dose of the drug would be life threatening. The oral LD₅₀ of the drug is

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650 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters, and greater than 1000
651 mg/kg in dogs.

652 Patients should be managed by symptomatic and supportive care following a NSAID
653 overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma
654 concentration of naproxen because of the high degree of its protein binding. Emesis
655 and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic
656 cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or
657 following a large overdose. Forced diuresis, alkalization of urine or hemoperfusion may
658 not be useful due to high protein binding.

659 **DOSAGE AND ADMINISTRATION**

660 **Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis:**

NAPROSYN	250 mg or 375 mg or 500 mg	twice daily twice daily twice daily
ANAPROX	275 mg (naproxen 250 mg with 25 mg sodium)	twice daily
ANAPROX DS	550 mg (naproxen 500 mg with 50 mg sodium)	twice daily
NAPROSYN Suspension	250 mg (10 mL/2 tsp) or 375 mg (15 mL/3 tsp) or 500 mg (20 mL/4 tsp)	twice daily twice daily twice daily
EC-NAPROSYN	375 mg or 500 mg	twice daily twice daily

661 To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet should not be
662 broken, crushed or chewed during ingestion.

663 During long-term administration, the dose of naproxen may be adjusted up or down
664 depending on the clinical response of the patient. A lower daily dose may suffice for
665 long-term administration. The morning and evening doses do not have to be equal in size
666 and the administration of the drug more frequently than twice daily is not necessary.

667 In patients who tolerate lower doses well, the dose may be increased to naproxen 1500
668 mg per day for limited periods of up to 6 months when a higher level of anti-
669 inflammatory/analgesic activity is required. When treating such patients with naproxen
670 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset
671 the potential increased risk (see CLINICAL PHARMACOLOGY and
672 INDIVIDUALIZATION OF DOSAGE).

673 **Geriatric Patients:** Studies indicate that although total plasma concentration of naproxen
674 is unchanged, the unbound plasma fraction of naproxen is increased in the elderly.
675 Caution is advised when high doses are required and some adjustment of dosage may be
676 required in elderly patients. As with other drugs used in the elderly, it is prudent to use
677 the lowest effective dose.

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678 **Juvenile Arthritis:** The recommended total daily dose of naproxen is approximately 10
679 mg/kg given in 2 divided doses (ie, 5 mg/kg given twice a day). A measuring cup marked
680 in 1/2 teaspoon and 2.5 milliliter increments is provided with the NAPROSYN
681 Suspension. The following table may be used as a guide for dosing of NAPROSYN
682 Suspension:

683	Patient's Weight	Dose	Administered as
684	13 kg (29 lb)	62.5 mg bid	2.5 mL (1/2 tsp) twice daily
685	25 kg (55 lb)	125 mg bid	5.0 mL (1 tsp) twice daily
686	38 kg (84 lb)	187.5 mg bid	7.5 mL (1 1/2 tsp) twice daily

687 **Management of Pain, Primary Dysmenorrhea and Acute Tendonitis and Bursitis:** The
688 recommended starting dose is 550 mg of naproxen sodium as ANAPROX/ANAPROX
689 DS followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The
690 initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the
691 total daily dose should not exceed 1100 mg of naproxen sodium. NAPROSYN may also
692 be used but EC-NAPROSYN is not recommended for initial treatment of acute pain
693 because absorption of naproxen is delayed compared to other naproxen-containing
694 products (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE and
695 INDIVIDUALIZATION OF DOSAGE).

696 **Acute Gout:** The recommended starting dose is 750 mg of NAPROSYN followed by 250
697 mg every 8 hours until the attack has subsided. ANAPROX may also be used at a starting
698 dose of 825 mg followed by 275 mg every 8 hours. EC-NAPROSYN is not
699 recommended because of the delay in absorption (see CLINICAL PHARMACOLOGY).

700 **HOW SUPPLIED**

701 **NAPROSYN Tablets:** 250 mg: round, yellow, biconvex, engraved with NPR LE 250 on
702 one side and scored on the other. Packaged in light-resistant bottles of 100.

703 100's (bottle): NDC 0004-6313-01.

704 375 mg: pink, biconvex oval, engraved with NPR LE 375 on one side. Packaged in light-
705 resistant bottles of 100 and 500.

706 100's (bottle): NDC 0004-6314-01; 500's (bottle): NDC 0004-6314-14.

707 500 mg: yellow, capsule-shaped, engraved with NPR LE 500 on one side and scored on
708 the other. Packaged in light-resistant bottles of 100 and 500.

709 100's (bottle): NDC 0004-6316-01; 500's (bottle): NDC 0004-6316-14.

710 Store at 15° to 30°C (59° to 86°F) in well-closed containers; dispense in light-resistant
711 containers.

712 **NAPROSYN Suspension:** 125 mg/5 mL (contains 39 mg sodium, about 1.5
713 mEq/teaspoon): Available in 1 pint (473 mL) light-resistant bottles (NDC 0004-0028-28).

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714 Store at 15° to 30°C (59° to 86°F); avoid excessive heat, above 40°C (104°F). Dispense
715 in light-resistant containers.

716 **EC-NAPROSYN Delayed-Release Tablets:** 375 mg: white, capsule-shaped, imprinted
717 with EC-NAPROSYN on one side and 375 on the other. Packaged in light-resistant
718 bottles of 100.

719 100's (bottle): NDC 0004-6415-01.

720 500 mg: white, capsule-shaped, imprinted with EC-NAPROSYN on one side and 500 on
721 the other. Packaged in light-resistant bottles of 100.

722 100's (bottle): NDC 0004-6416-01.

723 Store at 15° to 30°C (59° to 86°F) in well-closed containers; dispense in light-resistant
724 containers.

725 **ANAPROX Tablets:** Naproxen sodium 275 mg: light blue, oval-shaped, engraved with
726 NPS-275 on one side. Packaged in bottles of 100.

727 100's (bottle): NDC 0004-6202-01.

728 Store at 15° to 30°C (59° to 86°F) in well-closed containers.

729 **ANAPROX DS Tablets:** Naproxen sodium 550 mg: dark blue, oblong-shaped, engraved
730 with NPS 550 on one side and scored on both sides. Packaged in bottles of 100 and 500.

731 100's (bottle): NDC 0004-6203-01; 500's (bottle): NDC 0004-6203-14.

732 Store at 15° to 30°C (59° to 86°F) in well-closed containers.

733 * ALEVE is a registered trademark of Bayer-Roche L.L.C.

734

735 Distributed by:



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

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738 Revised: Month/Year

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