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2 **EC-NAPROSYN (naproxen delayed-release tablets)**
3 **NAPROSYN (naproxen tablets)**
4 **ANAPROX /ANAPROX DS (naproxen sodium tablets)**
5 **NAPROSYN (naproxen suspension)**

6 **R_x only**

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**).
- Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

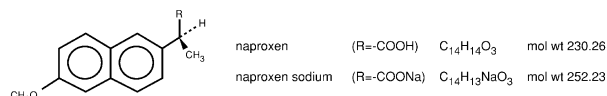
Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

7 **DESCRIPTION**

8 Naproxen is a propionic acid derivative related to the arylacetic acid group of
9 nonsteroidal anti-inflammatory drugs.

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



14
15 Naproxen has a molecular weight of 230.26 and a molecular formula of
16 C₁₄H₁₄O₃. Naproxen sodium has a molecular weight of 252.23 and a
17 molecular formula of C₁₄H₁₃NaO₃.

18 Naproxen is an odorless, white to off-white crystalline substance. It is lipid-
19 soluble, practically insoluble in water at low pH and freely soluble in water at
20 high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6

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21 to 1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely
22 soluble in water at neutral pH.

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

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

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

46 NAPROSYN (naproxen suspension) is available as a light orange-colored
47 opaque oral suspension containing 125 mg/5 mL of naproxen in a vehicle
48 containing sucrose, magnesium aluminum silicate, sorbitol solution and
49 sodium chloride (39 mg/5 mL, 1.5 mEq), methylparaben, fumaric acid, FD&C
50 Yellow No. 6, imitation pineapple flavor, imitation orange flavor and purified
51 water. The pH of the suspension ranges from 2.2 to 3.7.

52 **CLINICAL PHARMACOLOGY**

53 **Pharmacodynamics**

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

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

60 **Pharmacokinetics**

61 Naproxen and naproxen sodium are rapidly and completely absorbed from the
62 gastrointestinal tract with an in vivo bioavailability of 95%. The different
63 dosage forms of NAPROSYN are bioequivalent in terms of extent of
64 absorption (AUC) and peak concentration (C_{max}); however, the products do
65 differ in their pattern of absorption. These differences between naproxen
66 products are related to both the chemical form of naproxen used and its
67 formulation. Even with the observed differences in pattern of absorption, the
68 elimination half-life of naproxen is unchanged across products ranging from
69 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and
70 the degree of naproxen accumulation is consistent with this half-life. This
71 suggests that the differences in pattern of release play only a negligible role in
72 the attainment of steady-state plasma levels.

73 **Absorption**

74 *Immediate Release*

75 After administration of NAPROSYN tablets, peak plasma levels are attained
76 in 2 to 4 hours. After oral administration of ANAPROX, peak plasma levels
77 are attained in 1 to 2 hours. The difference in rates between the two products
78 is due to the increased aqueous solubility of the sodium salt of naproxen used
79 in ANAPROX. Peak plasma levels of naproxen given as NAPROSYN
80 Suspension are attained in 1 to 4 hours.

81 *Delayed Release*

82 EC-NAPROSYN is designed with a pH-sensitive coating to provide a barrier
83 to disintegration in the acidic environment of the stomach and to lose integrity
84 in the more neutral environment of the small intestine. The enteric polymer
85 coating selected for EC-NAPROSYN dissolves above pH 6. When EC-
86 NAPROSYN was given to fasted subjects, peak plasma levels were attained
87 about 4 to 6 hours following the first dose (range: 2 to 12 hours). An in vivo
88 study in man using radiolabeled EC-NAPROSYN tablets demonstrated that
89 EC-NAPROSYN dissolves primarily in the small intestine rather than in the
90 stomach, so the absorption of the drug is delayed until the stomach is emptied.

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

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| | 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%) |

95 *Mean value (coefficient of variation)

96 *Antacid Effects*

97 When EC-NAPROSYN was given as a single dose with antacid (54 mEq
98 buffering capacity), the peak plasma levels of naproxen were unchanged, but
99 the time to peak was reduced (mean T_{max} fasted 5.6 hours, mean T_{max} with
100 antacid 5 hours), although not significantly.

101 *Food Effects*

102 When EC-NAPROSYN was given as a single dose with food, peak plasma
103 levels in most subjects were achieved in about 12 hours (range: 4 to 24 hours).
104 Residence time in the small intestine until disintegration was independent of
105 food intake. The presence of food prolonged the time the tablets remained in
106 the stomach, time to first detectable serum naproxen levels, and time to
107 maximal naproxen levels (T_{max}), but did not affect peak naproxen levels
108 (C_{max}).

109 *Distribution*

110 Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels
111 naproxen is greater than 99% albumin-bound. At doses of naproxen greater
112 than 500 mg/day there is less than proportional increase in plasma levels due
113 to an increase in clearance caused by saturation of plasma protein binding at
114 higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and
115 1500 mg daily doses of naproxen, respectively). The naproxen anion has been
116 found in the milk of lactating women at a concentration equivalent to
117 approximately 1% of maximum naproxen concentration in plasma (see
118 **PRECAUTIONS: Nursing Mothers**).

119 *Metabolism*

120 Naproxen is extensively metabolized in the liver to 6-0-desmethyl naproxen,
121 and both parent and metabolites do not induce metabolizing enzymes. Both
122 naproxen and 6-0-desmethyl naproxen are further metabolized to their
123 respective acylglucuronide conjugated metabolites.

124 *Excretion*

125 The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the
126 naproxen from any dose is excreted in the urine, primarily as naproxen (<1%),
127 6-0-desmethyl naproxen (<1%) or their conjugates (66% to 92%). The plasma

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128 half-life of the naproxen anion in humans ranges from 12 to 17 hours. The
129 corresponding half-lives of both naproxen's metabolites and conjugates are
130 shorter than 12 hours, and their rates of excretion have been found to coincide
131 closely with the rate of naproxen disappearance from the plasma. Small
132 amounts, 3% or less of the administered dose, are excreted in the feces. In
133 patients with renal failure metabolites may accumulate (see **WARNINGS:**
134 **Renal Effects**).

135 Special Populations

136 *Pediatric Patients*

137 In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels
138 following a 5 mg/kg single dose of naproxen suspension (see **DOSAGE AND**
139 **ADMINISTRATION**) were found to be similar to those found in normal
140 adults following a 500 mg dose. The terminal half-life appears to be similar in
141 pediatric and adult patients. Pharmacokinetic studies of naproxen were not
142 performed in pediatric patients younger than 5 years of age. Pharmacokinetic
143 parameters appear to be similar following administration of naproxen
144 suspension or tablets in pediatric patients. EC-NAPROSYN has not been
145 studied in subjects under the age of 18.

146 *Geriatric Patients*

147 Studies indicate that although total plasma concentration of naproxen is
148 unchanged, the unbound plasma fraction of naproxen is increased in the
149 elderly, although the unbound fraction is <1% of the total naproxen
150 concentration. Unbound trough naproxen concentrations in elderly subjects
151 have been reported to range from 0.12% to 0.19% of total naproxen
152 concentration, compared with 0.05% to 0.075% in younger subjects. The
153 clinical significance of this finding is unclear, although it is possible that the
154 increase in free naproxen concentration could be associated with an increase
155 in the rate of adverse events per a given dosage in some elderly patients.

156 *Race*

157 Pharmacokinetic differences due to race have not been studied.

158 *Hepatic Insufficiency*

159 Naproxen pharmacokinetics has not been determined in subjects with hepatic
160 insufficiency.

161 *Renal Insufficiency*

162 Naproxen pharmacokinetics has not been determined in subjects with renal
163 insufficiency. Given that naproxen, its metabolites and conjugates are
164 primarily excreted by the kidney, the potential exists for naproxen metabolites

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165 to accumulate in the presence of renal insufficiency. Elimination of naproxen
166 is decreased in patients with severe renal impairment. Naproxen-containing
167 products are not recommended for use in patients with moderate to severe and
168 severe renal impairment (creatinine clearance <30 mL/min) (see
169 **WARNINGS: Renal Effects**).

170 **CLINICAL STUDIES**

171 **General Information**

172 Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis,
173 juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute
174 gout. Improvement in patients treated for rheumatoid arthritis was
175 demonstrated by a reduction in joint swelling, a reduction in duration of
176 morning stiffness, a reduction in disease activity as assessed by both the
177 investigator and patient, and by increased mobility as demonstrated by a
178 reduction in walking time. Generally, response to naproxen has not been
179 found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

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

185 In a clinical trial comparing standard formulations of naproxen 375 mg bid
186 (750 mg a day) vs 750 mg bid (1500 mg/day), 9 patients in the 750 mg group
187 terminated prematurely because of adverse events. Nineteen patients in the
188 1500 mg group terminated prematurely because of adverse events. Most of
189 these adverse events were gastrointestinal events.

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

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

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

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203 Naproxen has been studied in patients with mild to moderate pain secondary
204 to postoperative, orthopedic, postpartum episiotomy and uterine contraction
205 pain and dysmenorrhea. Onset of pain relief can begin within 1 hour in
206 patients taking naproxen and within 30 minutes in patients taking naproxen
207 sodium. Analgesic effect was shown by such measures as reduction of pain
208 intensity scores, increase in pain relief scores, decrease in numbers of patients
209 requiring additional analgesic medication, and delay in time to remediation.
210 The analgesic effect has been found to last for up to 12 hours.

211 Naproxen may be used safely in combination with gold salts and/or
212 corticosteroids; however, in controlled clinical trials, when added to the
213 regimen of patients receiving corticosteroids, it did not appear to cause greater
214 improvement over that seen with corticosteroids alone. Whether naproxen has
215 a “steroid-sparing” effect has not been adequately studied. When added to the
216 regimen of patients receiving gold salts, naproxen did result in greater
217 improvement. Its use in combination with salicylates is not recommended
218 because there is evidence that aspirin increases the rate of excretion of
219 naproxen and data are inadequate to demonstrate that naproxen and aspirin
220 produce greater improvement over that achieved with aspirin alone. In
221 addition, as with other NSAIDs, the combination may result in higher
222 frequency of adverse events than demonstrated for either product alone.

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

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

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

240 **Geriatric Patients**

241 The hepatic and renal tolerability of long-term naproxen administration was
242 studied in two double-blind clinical trials involving 586 patients. Of the

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243 patients studied, 98 patients were age 65 and older and 10 of the 98 patients
244 were age 75 and older. Naproxen was administered at doses of 375 mg twice
245 daily or 750 mg twice daily for up to 6 months. Transient abnormalities of
246 laboratory tests assessing hepatic and renal function were noted in some
247 patients, although there were no differences noted in the occurrence of
248 abnormal values among different age groups.

249 **INDICATIONS AND USAGE**

250 Carefully consider the potential benefits and risks of NAPROSYN, EC-
251 NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension and
252 other treatment options before deciding to use NAPROSYN, EC-
253 NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension. Use
254 the lowest effective dose for the shortest duration consistent with individual
255 patient treatment goals (see **WARNINGS**).

256 Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or
257 NAPROSYN Suspension is indicated:

- 258 • For the relief of the signs and symptoms of rheumatoid arthritis
- 259 • For the relief of the signs and symptoms of osteoarthritis
- 260 • For the relief of the signs and symptoms of ankylosing spondylitis
- 261 • For the relief of the signs and symptoms of juvenile arthritis

262 Naproxen as NAPROSYN Suspension is recommended for juvenile
263 rheumatoid arthritis in order to obtain the maximum dosage flexibility based
264 on the patient's weight.

265 Naproxen as NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN
266 Suspension is also indicated:

- 267 • For relief of the signs and symptoms of tendonitis
- 268 • For relief of the signs and symptoms of bursitis
- 269 • For relief of the signs and symptoms of acute gout
- 270 • For the management of pain
- 271 • For the management of primary dysmenorrhea

272 EC-NAPROSYN is not recommended for initial treatment of acute pain
273 because the absorption of naproxen is delayed compared to absorption from
274 other naproxen-containing products (see **CLINICAL PHARMACOLOGY**
275 and **DOSAGE AND ADMINISTRATION**).

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276 **CONTRAINDICATIONS**

277 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
278 NAPROSYN Suspension are contraindicated in patients with known
279 hypersensitivity to naproxen and naproxen sodium.

280 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
281 NAPROSYN Suspension should not be given to patients who have
282 experienced asthma, urticaria, or allergic-type reactions after taking aspirin or
283 other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs
284 have been reported in such patients (see **WARNINGS: Anaphylactoid**
285 **Reactions** and **PRECAUTIONS: Preexisting Asthma**).

286 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
287 NAPROSYN Suspension are contraindicated for the treatment of peri-
288 operative pain in the setting of coronary artery bypass graft (CABG) surgery
289 (see **WARNINGS**).

290 **WARNINGS**

291 **CARDIOVASCULAR EFFECTS**

292 **Cardiovascular Thrombotic Events**

293 Clinical trials of several COX-2 selective and nonselective NSAIDs of up to
294 three years duration have shown an increased risk of serious cardiovascular
295 (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal.
296 All NSAIDs, both COX-2 selective and nonselective, may have a similar risk.
297 Patients with known CV disease or risk factors for CV disease may be at
298 greater risk. To minimize the potential risk for an adverse CV event in patients
299 treated with an NSAID, the lowest effective dose should be used for the
300 shortest duration possible. Physicians and patients should remain alert for the
301 development of such events, even in the absence of previous CV symptoms.
302 Patients should be informed about the signs and/or symptoms of serious CV
303 events and the steps to take if they occur.

304 There is no consistent evidence that concurrent use of aspirin mitigates the
305 increased risk of serious CV thrombotic events associated with NSAID use.
306 The concurrent use of aspirin and an NSAID does increase the risk of serious
307 GI events (see **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and**
308 **Perforation**).

309 Two large, controlled, clinical trials of a COX-2 selective NSAID for the
310 treatment of pain in the first 10-14 days following CABG surgery found an
311 increased incidence of myocardial infarction and stroke (see
312 **CONTRAINDICATIONS**).

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313 **Hypertension**

314 NSAIDs, including NAPROSYN, EC-NAPROSYN, ANAPROX,
315 ANAPROX DS and NAPROSYN Suspension, can lead to onset of new
316 hypertension or worsening of pre-existing hypertension, either of which may
317 contribute to the increased incidence of CV events. Patients taking thiazides or
318 loop diuretics may have impaired response to these therapies when taking
319 NSAIDs. NSAIDs, including NAPROSYN, EC-NAPROSYN, ANAPROX,
320 ANAPROX DS and NAPROSYN Suspension, should be used with caution in
321 patients with hypertension. Blood pressure (BP) should be monitored closely
322 during the initiation of NSAID treatment and throughout the course of
323 therapy.

324 **Congestive Heart Failure and Edema**

325 Fluid retention, edema, and peripheral edema have been observed in some
326 patients taking NSAIDs. NAPROSYN, EC-NAPROSYN, ANAPROX,
327 ANAPROX DS and NAPROSYN Suspension should be used with caution in
328 patients with fluid retention, hypertension, or heart failure. Since each
329 ANAPROX or ANAPROX DS tablet contains 25 mg or 50 mg of sodium
330 (about 1 mEq per each 250 mg of naproxen), and each teaspoonful of
331 NAPROSYN Suspension contains 39 mg (about 1.5 mEq per each 125 mg of
332 naproxen) of sodium, this should be considered in patients whose overall
333 intake of sodium must be severely restricted.

334 **Gastrointestinal Effects – Risk of Ulceration, Bleeding, and**
335 **Perforation**

336 NSAIDs, including NAPROSYN, EC-NAPROSYN, ANAPROX,
337 ANAPROX DS and NAPROSYN Suspension, can cause serious
338 gastrointestinal (GI) adverse events including inflammation, bleeding,
339 ulceration, and perforation of the stomach, small intestine, or large intestine,
340 which can be fatal.

341 These serious adverse events can occur at any time, with or without warning
342 symptoms, in patients treated with NSAIDs. Only one in five patients, who
343 develop a serious upper GI adverse event on NSAID therapy, is symptomatic.
344 Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in
345 approximately 1% of patients treated for 3-6 months, and in about 2-4% of
346 patients treated for one year. These trends continue with longer duration of
347 use, increasing the likelihood of developing a serious GI event at some time
348 during the course of therapy. However, even short-term therapy is not without
349 risk. The utility of periodic laboratory monitoring has not been demonstrated,
350 nor has it been adequately assessed. Only 1 in 5 patients who develop a
351 serious upper GI adverse event on NSAID therapy is symptomatic.

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352 NSAIDs should be prescribed with extreme caution in those with a prior
353 history of ulcer disease or gastrointestinal bleeding. Patients with a prior
354 history of peptic ulcer disease and/or gastrointestinal bleeding who use
355 NSAIDs have a greater than 10-fold increased risk for developing a GI bleed
356 compared to patients with neither of these risk factors. Other factors that
357 increase the risk for GI bleeding in patients treated with NSAIDs include
358 concomitant use of oral corticosteroids or anticoagulants, longer duration of
359 NSAID therapy, smoking, use of alcohol, older age, and poor general health
360 status. Most spontaneous reports of fatal GI events are in elderly or debilitated
361 patients and therefore, special care should be taken in treating this population.
362 To minimize the potential risk for an adverse GI event in patients treated with
363 an NSAID, the lowest effective dose should be used for the shortest possible
364 duration. Patients and physicians should remain alert for signs and symptoms
365 of GI ulceration and bleeding during NSAID therapy and promptly initiate
366 additional evaluation and treatment if a serious GI adverse event is suspected.
367 This should include discontinuation of the NSAID until a serious GI adverse
368 event is ruled out. For high risk patients, alternate therapies that do not
369 involve NSAIDs should be considered.

370 Epidemiological studies, both of the case-control and cohort design, have
371 demonstrated an association between use of psychotropic drugs that interfere
372 with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
373 In two studies, concurrent use of an NSAID or aspirin potentiated the risk of
374 bleeding (see **PRECAUTIONS: Drug Interactions**). Although these studies
375 focused on upper gastrointestinal bleeding, there is reason to believe that
376 bleeding at other sites may be similarly potentiated.

377 NSAIDs should be given with care to patients with a history of inflammatory
378 bowel disease (ulcerative colitis, Crohn's disease) as their condition may be
379 exacerbated.

380 **Renal Effects**

381 Long-term administration of NSAIDs has resulted in renal papillary necrosis
382 and other renal injury. Renal toxicity has also been seen in patients in whom
383 renal prostaglandins have a compensatory role in the maintenance of renal
384 perfusion. In these patients, administration of a nonsteroidal
385 anti-inflammatory drug may cause a dose-dependent reduction in
386 prostaglandin formation and, secondarily, in renal blood flow, which may
387 precipitate overt renal decompensation. Patients at greatest risk of this
388 reaction are those with impaired renal function, hypovolemia, heart failure,
389 liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors,
390 and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug
391 therapy is usually followed by recovery to the pretreatment state (see
392 **WARNINGS: Advanced Renal Disease**).

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393 **Advanced Renal Disease**

394 No information is available from controlled clinical studies regarding the use
395 of NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or
396 NAPROSYN Suspension in patients with advanced renal disease. Therefore,
397 treatment with NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS
398 and NAPROSYN Suspension is not recommended in these patients with
399 advanced renal disease. If NAPROSYN, EC-NAPROSYN, ANAPROX,
400 ANAPROX DS or NAPROSYN Suspension therapy must be initiated, close
401 monitoring of the patient's renal function is advisable.

402 **Anaphylactoid Reactions**

403 As with other NSAIDs, anaphylactoid reactions may occur in patients without
404 known prior exposure to NAPROSYN, EC-NAPROSYN, ANAPROX,
405 ANAPROX DS or NAPROSYN Suspension. NAPROSYN, EC-
406 NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension
407 should not be given to patients with the aspirin triad. This symptom complex
408 typically occurs in asthmatic patients who experience rhinitis with or without
409 nasal polyps, or who exhibit severe, potentially fatal bronchospasm after
410 taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and
411 **PRECAUTIONS: Preexisting Asthma**). Emergency help should be sought
412 in cases where an anaphylactoid reaction occurs. Anaphylactoid reactions, like
413 anaphylaxis, may have a fatal outcome.

414 **Skin Reactions**

415 NSAIDs, including NAPROSYN, EC-NAPROSYN, ANAPROX,
416 ANAPROX DS and NAPROSYN Suspension, can cause serious skin adverse
417 events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and
418 toxic epidermal necrolysis (TEN), which can be fatal. These serious events
419 may occur without warning. Patients should be informed about the signs and
420 symptoms of serious skin manifestations and use of the drug should be
421 discontinued at the first appearance of skin rash or any other sign of
422 hypersensitivity.

423 **Pregnancy**

424 In late pregnancy, as with other NSAIDs, NAPROSYN, EC-NAPROSYN,
425 ANAPROX, ANAPROX DS and NAPROSYN Suspension should be avoided
426 because it may cause premature closure of the ductus arteriosus.

427 **PRECAUTIONS**

428 **General**

429 **Naproxen-containing products such as NAPROSYN, EC-NAPROSYN,**
430 **ANAPROX, ANAPROX DS, NAPROSYN SUSPENSION, ALEVE®, and**

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431 **other naproxen products should not be used concomitantly since they all**
432 **circulate in the plasma as the naproxen anion.**

433 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
434 NAPROSYN Suspension cannot be expected to substitute for corticosteroids
435 or to treat corticosteroid insufficiency. Abrupt discontinuation of
436 corticosteroids may lead to disease exacerbation. Patients on prolonged
437 corticosteroid therapy should have their therapy tapered slowly if a decision is
438 made to discontinue corticosteroids and the patient should be observed closely
439 for any evidence of adverse effects, including adrenal insufficiency and
440 exacerbation of symptoms of arthritis.

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

443 The pharmacological activity of NAPROSYN, EC-NAPROSYN,
444 ANAPROX, ANAPROX DS and NAPROSYN Suspension in reducing fever
445 and inflammation may diminish the utility of these diagnostic signs in
446 detecting complications of presumed noninfectious, noninflammatory painful
447 conditions.

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

451 **Hepatic Effects**

452 Borderline elevations of one or more liver tests may occur in up to 15% of
453 patients taking NSAIDs including NAPROSYN, EC-NAPROSYN,
454 ANAPROX, ANAPROX DS and NAPROSYN Suspension. Hepatic
455 abnormalities may be the result of hypersensitivity rather than direct toxicity.
456 These laboratory abnormalities may progress, may remain essentially
457 unchanged, or may be transient with continued therapy. The SGPT (ALT) test
458 is probably the most sensitive indicator of liver dysfunction. Notable
459 elevations of ALT or AST (approximately three or more times the upper limit
460 of normal) have been reported in approximately 1% of patients in clinical
461 trials with NSAIDs. In addition, rare cases of severe hepatic reactions,
462 including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic
463 failure, some of them with fatal outcomes have been reported.

464 A patient with symptoms and/or signs suggesting liver dysfunction, or in
465 whom an abnormal liver test has occurred, should be evaluated for evidence
466 of the development of more severe hepatic reaction while on therapy with
467 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or
468 NAPROSYN Suspension.

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469 If clinical signs and symptoms consistent with liver disease develop, or if
470 systemic manifestations occur (eg, eosinophilia, rash, etc.), NAPROSYN, EC-
471 NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension
472 should be discontinued.

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

479 **Hematological Effects**

480 Anemia is sometimes seen in patients receiving NSAIDs, including
481 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
482 NAPROSYN Suspension. This may be due to fluid retention, occult or gross
483 GI blood loss, or an incompletely described effect upon erythropoiesis.
484 Patients on long-term treatment with NSAIDs, including NAPROSYN, EC-
485 NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension,
486 should have their hemoglobin or hematocrit checked if they exhibit any signs
487 or symptoms of anemia.

488 NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding
489 time in some patients. Unlike aspirin, their effect on platelet function is
490 quantitatively less, of shorter duration, and reversible. Patients receiving either
491 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or
492 NAPROSYN Suspension who may be adversely affected by alterations in
493 platelet function, such as those with coagulation disorders or patients
494 receiving anticoagulants, should be carefully monitored.

495 **Preexisting Asthma**

496 Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in
497 patients with aspirin-sensitive asthma has been associated with severe
498 bronchospasm, which can be fatal. Since cross reactivity, including
499 bronchospasm, between aspirin and other nonsteroidal anti-inflammatory
500 drugs has been reported in such aspirin-sensitive patients, NAPROSYN, EC-
501 NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension
502 should not be administered to patients with this form of aspirin sensitivity and
503 should be used with caution in patients with preexisting asthma.

504 **Information for Patients**

505 **Patients should be informed of the following information before initiating**
506 **therapy with an NSAID and periodically during the course of ongoing**

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507 **therapy. Patients should also be encouraged to read the NSAID**
508 **Medication Guide that accompanies each prescription dispensed.**

- 509 1. NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
510 NAPROSYN Suspension, like other NSAIDs, may cause serious CV side
511 effects, such as MI or stroke, which may result in hospitalization and even
512 death. Although serious CV events can occur without warning symptoms,
513 patients should be alert for the signs and symptoms of chest pain,
514 shortness of breath, weakness, slurring of speech, and should ask for
515 medical advice when observing any indicative sign or symptoms. Patients
516 should be apprised of the importance of this follow-up (see **WARNINGS:**
517 **Cardiovascular Effects**).
- 518 2. NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
519 NAPROSYN Suspension, like other NSAIDs, can cause GI discomfort
520 and, rarely, serious GI side effects, such as ulcers and bleeding, which
521 may result in hospitalization and even death. Although serious GI tract
522 ulcerations and bleeding can occur without warning symptoms, patients
523 should be alert for the signs and symptoms of ulcerations and bleeding,
524 and should ask for medical advice when observing any indicative sign or
525 symptoms including epigastric pain, dyspepsia, melena, and hematemesis.
526 Patients should be apprised of the importance of this follow-up (see
527 **WARNINGS: Gastrointestinal Effects: Risk of Ulceration, Bleeding,**
528 **and Perforation**).
- 529 3. NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
530 NAPROSYN Suspension, like other NSAIDs, can cause serious skin side
531 effects such as exfoliative dermatitis, SJS, and TEN, which may result in
532 hospitalizations and even death. Although serious skin reactions may
533 occur without warning, patients should be alert for the signs and
534 symptoms of skin rash and blisters, fever, or other signs of
535 hypersensitivity such as itching, and should ask for medical advice when
536 observing any indicative signs or symptoms. Patients should be advised to
537 stop the drug immediately if they develop any type of rash and contact
538 their physicians as soon as possible.
- 539 4. Patients should promptly report signs or symptoms of unexplained weight
540 gain or edema to their physicians.
- 541 5. Patients should be informed of the warning signs and symptoms of
542 hepatotoxicity (eg, nausea, fatigue, lethargy, pruritus, jaundice, right upper
543 quadrant tenderness, and “flu-like” symptoms). If these occur, patients
544 should be instructed to stop therapy and seek immediate medical therapy.
- 545 6. Patients should be informed of the signs of an anaphylactoid reaction (eg,
546 difficulty breathing, swelling of the face or throat). If these occur, patients
547 should be instructed to seek immediate emergency help (see
548 **WARNINGS**).

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- 549 7. In late pregnancy, as with other NSAIDs, NAPROSYN, EC-NAPROSYN,
550 ANAPROX, ANAPROX DS and NAPROSYN Suspension should be
551 avoided because it may cause premature closure of the ductus arteriosus.
552 8. Caution should be exercised by patients whose activities require alertness
553 if they experience drowsiness, dizziness, vertigo or depression during
554 therapy with naproxen.

555 **Laboratory Tests**

556 Because serious GI tract ulcerations and bleeding can occur without warning
557 symptoms, physicians should monitor for signs or symptoms of GI bleeding.
558 Patients on long-term treatment with NSAIDs should have their CBC and a
559 chemistry profile checked periodically. If clinical signs and symptoms
560 consistent with liver or renal disease develop, systemic manifestations occur
561 (eg, eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen,
562 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
563 NAPROSYN Suspension should be discontinued.

564 **Drug Interactions**

565 ***ACE-inhibitors***

566 Reports suggest that NSAIDs may diminish the antihypertensive effect of
567 ACE-inhibitors. This interaction should be given consideration in patients
568 taking NSAIDs concomitantly with ACE-inhibitors.

569 ***Antacids and Sucralfate***

570 Concomitant administration of some antacids (magnesium oxide or aluminum
571 hydroxide) and sucralfate can delay the absorption of naproxen.

572 ***Aspirin***

573 When naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX
574 DS or NAPROSYN Suspension is administered with aspirin, its protein
575 binding is reduced, although the clearance of free NAPROSYN, EC-
576 NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension is
577 not altered. The clinical significance of this interaction is not known;
578 however, as with other NSAIDs, concomitant administration of naproxen and
579 naproxen sodium and aspirin is not generally recommended because of the
580 potential of increased adverse effects.

581 ***Cholestyramine***

582 As with other NSAIDs, concomitant administration of cholestyramine can
583 delay the absorption of naproxen.

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584 ***Diuretics***

585 Clinical studies, as well as postmarketing observations, have shown that
586 NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and
587 NAPROSYN Suspension can reduce the natriuretic effect of furosemide and
588 thiazides in some patients. This response has been attributed to inhibition of
589 renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the
590 patient should be observed closely for signs of renal failure (see
591 **WARNINGS: Renal Effects**), as well as to assure diuretic efficacy.

592 ***Lithium***

593 NSAIDs have produced an elevation of plasma lithium levels and a reduction
594 in renal lithium clearance. The mean minimum lithium concentration
595 increased 15% and the renal clearance was decreased by approximately 20%.
596 These effects have been attributed to inhibition of renal prostaglandin
597 synthesis by the NSAID. Thus, when NSAIDs and lithium are administered
598 concurrently, subjects should be observed carefully for signs of lithium
599 toxicity.

600 ***Methotrexate***

601 NSAIDs have been reported to competitively inhibit methotrexate
602 accumulation in rabbit kidney slices. Naproxen, naproxen sodium and other
603 nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular
604 secretion of methotrexate in an animal model. This may indicate that they
605 could enhance the toxicity of methotrexate. Caution should be used when
606 NSAIDs are administered concomitantly with methotrexate.

607 ***Warfarin***

608 The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that
609 users of both drugs together have a risk of serious GI bleeding higher than
610 users of either drug alone. No significant interactions have been observed in
611 clinical studies with naproxen and coumarin-type anticoagulants. However,
612 caution is advised since interactions have been seen with other nonsteroidal
613 agents of this class. The free fraction of warfarin may increase substantially in
614 some subjects and naproxen interferes with platelet function.

615 ***Selective Serotonin Reuptake Inhibitors (SSRIs)***

616 There is an increased risk of gastrointestinal bleeding when selective serotonin
617 reuptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be
618 used when NSAIDs are administered concomitantly with SSRIs.

619 ***Other Information Concerning Drug Interactions***

620 Naproxen is highly bound to plasma albumin; it thus has a theoretical
621 potential for interaction with other albumin-bound drugs such as coumarin-

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622 type anticoagulants, sulphonylureas, hydantoin, other NSAIDs, and aspirin.
623 Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or
624 sulphonylurea should be observed for adjustment of dose if required.

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

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

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

632 Drug/Laboratory Test Interaction

633 Naproxen may decrease platelet aggregation and prolong bleeding time. This
634 effect should be kept in mind when bleeding times are determined.

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

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

644 Carcinogenesis

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

649 Pregnancy

650 Teratogenic Effects

651 *Pregnancy Category C*

652 Reproduction studies have been performed in rats at 20 mg/kg/day
653 (125 mg/m²/day, 0.23 times the human systemic exposure), rabbits at 20
654 mg/kg/day (220 mg/m²/day, 0.27 times the human systemic exposure), and
655 mice at 170 mg/kg/day (510 mg/m²/day, 0.28 times the human systemic
656 exposure) with no evidence of impaired fertility or harm to the fetus due to the
657 drug. However, animal reproduction studies are not always predictive of

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658 human response. There are no adequate and well-controlled studies in
659 pregnant women. NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX
660 DS and NAPROSYN Suspension should be used in pregnancy only if the
661 potential benefit justifies the potential risk to the fetus.

662 **Nonteratogenic Effects**

663 There is some evidence to suggest that when inhibitors of prostaglandin
664 synthesis are used to delay preterm labor there is an increased risk of neonatal
665 complications such as necrotizing enterocolitis, patent ductus arteriosus and
666 intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay
667 parturition has been associated with persistent pulmonary hypertension, renal
668 dysfunction and abnormal prostaglandin E levels in preterm infants. Because
669 of the known effects of nonsteroidal anti-inflammatory drugs on the fetal
670 cardiovascular system (closure of ductus arteriosus), use during pregnancy
671 (particularly late pregnancy) should be avoided.

672 **Labor and Delivery**

673 In rat studies with NSAIDs, as with other drugs known to inhibit
674 prostaglandin synthesis, an increased incidence of dystocia, delayed
675 parturition, and decreased pup survival occurred. Naproxen-containing
676 products are not recommended in labor and delivery because, through its
677 prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal
678 circulation and inhibit uterine contractions, thus increasing the risk of uterine
679 hemorrhage. The effects of NAPROSYN, EC-NAPROSYN, ANAPROX,
680 ANAPROX DS and NAPROSYN Suspension on labor and delivery in
681 pregnant women are unknown.

682 **Nursing Mothers**

683 The naproxen anion has been found in the milk of lactating women at a
684 concentration equivalent to approximately 1% of maximum naproxen
685 concentration in plasma. Because of the possible adverse effects of
686 prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be
687 avoided.

688 **Pediatric Use**

689 Safety and effectiveness in pediatric patients below the age of 2 years have
690 not been established. Pediatric dosing recommendations for juvenile arthritis
691 are based on well-controlled studies (see **DOSAGE AND**
692 **ADMINISTRATION**). There are no adequate effectiveness or dose-response
693 data for other pediatric conditions, but the experience in juvenile arthritis and
694 other use experience have established that single doses of 2.5 to 5 mg/kg (as
695 naproxen suspension, see **DOSAGE AND ADMINISTRATION**), with total

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696 daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients
697 over 2 years of age.

698 **Geriatric Use**

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

704 Experience indicates that geriatric patients may be particularly sensitive to
705 certain adverse effects of nonsteroidal anti-inflammatory drugs. Elderly or
706 debilitated patients seem to tolerate peptic ulceration or bleeding less well
707 when these events do occur. Most spontaneous reports of fatal GI events are in
708 the geriatric population (see **WARNINGS**).

709 Naproxen is known to be substantially excreted by the kidney, and the risk of
710 toxic reactions to this drug may be greater in patients with impaired renal
711 function. Because elderly patients are more likely to have decreased renal
712 function, care should be taken in dose selection, and it may be useful to
713 monitor renal function. Geriatric patients may be at a greater risk for the
714 development of a form of renal toxicity precipitated by reduced prostaglandin
715 formation during administration of nonsteroidal anti-inflammatory drugs (see
716 **WARNINGS: Renal Effects**).

717 **ADVERSE REACTIONS**

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

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

728 In controlled clinical trials with about 80 pediatric patients and in well-
729 monitored, open-label studies with about 400 pediatric patients with juvenile
730 arthritis treated with naproxen, the incidence of rash and prolonged bleeding
731 times were increased, the incidence of gastrointestinal and central nervous
732 system reactions were about the same, and the incidence of other reactions
733 were lower in pediatric patients than in adults.

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

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

738 **Central Nervous System:** headache*, dizziness*, drowsiness*,
739 lightheadedness, vertigo

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

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

743 **Cardiovascular:** edema*, palpitations

744 **General:** dyspnea*, thirst

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

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

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

751 **General:** abnormal renal function, anemia, elevated liver enzymes, increased
752 bleeding time, rashes

753 The following are additional adverse experiences reported in <1% of patients
754 taking naproxen during clinical trials and through postmarketing reports.
755 Those adverse reactions observed through postmarketing reports are italicized.

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

758 **Cardiovascular:** *congestive heart failure, vasculitis, hypertension, pulmonary*
759 *edema*

760 **Gastrointestinal:** *gastrointestinal bleeding and/or perforation, hematemesis,*
761 *pancreatitis, vomiting, colitis, exacerbation of inflammatory bowel disease*
762 *(ulcerative colitis, Crohn's disease), nonpeptic gastrointestinal ulceration,*
763 *ulcerative stomatitis, esophagitis, peptic ulceration*

764 **Hepatobiliary:** *jaundice, abnormal liver function tests, hepatitis (some cases*
765 *have been fatal)*

766 **Hemic and Lymphatic:** *eosinophilia, leucopenia, melena, thrombocytopenia,*
767 *agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia*

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

769 **Nervous System:** *inability to concentrate, depression, dream abnormalities,*
770 *insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive*
771 *dysfunction, convulsions*

772 **Respiratory:** *eosinophilic pneumonitis, asthma*

773 **Dermatologic:** *alopecia, urticaria, skin rashes, toxic epidermal necrolysis,*
774 *erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus,*
775 *pustular reaction, systemic lupus erythematoses, bullous reactions, including*
776 *Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity*
777 *reactions, including rare cases resembling porphyria cutanea tarda*
778 *(pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or*
779 *other symptoms suggestive of pseudoporphyria occur, treatment should be*
780 *discontinued and the patient monitored.*

781 **Special Senses:** *hearing impairment, corneal opacity, papillitis, retrobulbar*
782 *optic neuritis, papilledema*

783 **Urogenital:** *glomerular nephritis, hematuria, hyperkalemia, interstitial*
784 *nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary*
785 *necrosis, raised serum creatinine*

786 **Reproduction (female):** *infertility*

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

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

791 **Cardiovascular:** *hypertension, tachycardia, syncope, arrhythmia,*
792 *hypotension, myocardial infarction*

793 **Gastrointestinal:** *dry mouth, esophagitis, gastric/peptic ulcers, gastritis,*
794 *glossitis, eructation*

795 **Hepatobiliary:** *hepatitis, liver failure*

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

797 **Metabolic and Nutritional:** *weight changes*

798 **Nervous System:** *anxiety, asthenia, confusion, nervousness, paresthesia,*
799 *somnolence, tremors, convulsions, coma, hallucinations*

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

801 **Dermatologic:** *exfoliative dermatitis*

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

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

804 **OVERDOSAGE**

805 **Symptoms and Signs**

806 Significant naproxen overdose may be characterized by lethargy, dizziness,
807 drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion,
808 nausea, transient alterations in liver function, hypoprothrombinemia, renal
809 dysfunction, metabolic acidosis, apnea, disorientation or vomiting.
810 Gastrointestinal bleeding can occur. Hypertension, acute renal failure,
811 respiratory depression, and coma may occur, but are rare. Anaphylactoid
812 reactions have been reported with therapeutic ingestion of NSAIDs, and may
813 occur following an overdose. Because naproxen sodium may be rapidly
814 absorbed, high and early blood levels should be anticipated. A few patients
815 have experienced convulsions, but it is not clear whether or not these were
816 drug-related. It is not known what dose of the drug would be life threatening.
817 The oral LD₅₀ of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110
818 mg/kg in hamsters, and greater than 1000 mg/kg in dogs.

819 **Treatment**

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

828 **DOSAGE AND ADMINISTRATION**

829 Carefully consider the potential benefits and risks of NAPROSYN, EC-
830 NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension and
831 other treatment options before deciding to use NAPROSYN, EC-
832 NAPROSYN, ANAPROX, ANAPROX DS and NAPROSYN Suspension.
833 Use the lowest effective dose for the shortest duration consistent with
834 individual patient treatment goals (see **WARNINGS**).

835 After observing the response to initial therapy with NAPROSYN, EC-
836 NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension, the
837 dose and frequency should be adjusted to suit an individual patient's needs.

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838 **Different dose strengths and formulations (ie, tablets, suspension) of the**
 839 **drug are not necessarily bioequivalent. This difference should be taken**
 840 **into consideration when changing formulation.**

841 Although NAPROSYN, NAPROSYN Suspension, EC-NAPROSYN,
 842 ANAPROX and ANAPROX DS all circulate in the plasma as naproxen, they
 843 have pharmacokinetic differences that may affect onset of action. Onset of
 844 pain relief can begin within 30 minutes in patients taking naproxen sodium
 845 and within 1 hour in patients taking naproxen. Because EC-NAPROSYN
 846 dissolves in the small intestine rather than in the stomach, the absorption of
 847 the drug is delayed compared to the other naproxen formulations (see
 848 **CLINICAL PHARMACOLOGY**).

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

854 **Geriatric Patients**

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

860 **Patients With Moderate to Severe Renal Impairment**

861 Naproxen-containing products are not recommended for use in patients with
 862 moderate to severe and severe renal impairment (creatinine clearance <30
 863 mL/min) (see **WARNINGS: Renal Effects**).

864 **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 |

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865 To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet
866 should not be broken, crushed or chewed during ingestion. NAPROSYN
867 Suspension should be shaken gently before use.

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

873 In patients who tolerate lower doses well, the dose may be increased to
874 naproxen 1500 mg/day for limited periods of up to 6 months when a higher
875 level of anti-inflammatory/analgesic activity is required. When treating such
876 patients with naproxen 1500 mg/day, the physician should observe sufficient
877 increased clinical benefits to offset the potential increased risk. The morning
878 and evening doses do not have to be equal in size and administration of the
879 drug more frequently than twice daily does not generally make a difference in
880 response (see **CLINICAL PHARMACOLOGY**).

881 Juvenile Arthritis

882 The use of NAPROSYN Suspension is recommended for juvenile arthritis in
883 children 2 years or older because it allows for more flexible dose titration
884 based on the child's weight. In pediatric patients, doses of 5 mg/kg/day
885 produced plasma levels of naproxen similar to those seen in adults taking 500
886 mg of naproxen (see **CLINICAL PHARMACOLOGY**).

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

| 892 | Patient's Weight | Dose | Administered as |
|-----|-------------------------|--------------|--------------------------------|
| 893 | 13 kg (29 lb) | 62.5 mg bid | 2.5 mL (1/2 tsp) twice daily |
| 894 | 25 kg (55 lb) | 125 mg bid | 5.0 mL (1 tsp) twice daily |
| 895 | 38 kg (84 lb) | 187.5 mg bid | 7.5 mL (1 1/2 tsp) twice daily |

**896 Management of Pain, Primary Dysmenorrhea, and Acute
897 Tendonitis and Bursitis**

898 The recommended starting dose is 550 mg of naproxen sodium as
899 ANAPROX/ANAPROX DS followed by 550 mg every 12 hours or 275 mg
900 every 6 to 8 hours as required. The initial total daily dose should not exceed
901 1375 mg of naproxen sodium. Thereafter, the total daily dose should not

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902 exceed 1100 mg of naproxen sodium. Because the sodium salt of naproxen is
903 more rapidly absorbed, ANAPROX/ANAPROX DS is recommended for the
904 management of acute painful conditions when prompt onset of pain relief is
905 desired. NAPROSYN may also be used but EC-NAPROSYN is not
906 recommended for initial treatment of acute pain because absorption of
907 naproxen is delayed compared to other naproxen-containing products (see
908 **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE**).

909 **Acute Gout**

910 The recommended starting dose is 750 mg of NAPROSYN followed by 250
911 mg every 8 hours until the attack has subsided. ANAPROX may also be used
912 at a starting dose of 825 mg followed by 275 mg every 8 hours. EC-
913 NAPROSYN is not recommended because of the delay in absorption (see
914 **CLINICAL PHARMACOLOGY**).

915 **HOW SUPPLIED**

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

919 100's (bottle): NDC 0004-6313-01.

920 375 mg: pink, biconvex oval, engraved with NPR LE 375 on one side.
921 Packaged in light-resistant bottles of 100.

922 100's (bottle): NDC 0004-6314-01.

923 500 mg: yellow, capsule-shaped, engraved with NPR LE 500 on one side and
924 scored on the other. Packaged in light-resistant bottles of 100.

925 100's (bottle): NDC 0004-6316-01.

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

928 **NAPROSYN Suspension:** 125 mg/5 mL (contains 39 mg sodium, about 1.5
929 mEq/teaspoon): Available in 1 pint (473 mL) light-resistant bottles (NDC
930 0004-0028-28).

931 Store at 15° to 30°C (59° to 86°F); avoid excessive heat, above 40°C (104°F).
932 Dispense in light-resistant containers. Shake gently before use.

933 **EC-NAPROSYN Delayed-Release Tablets:** 375 mg: white, oval biconvex
934 coated tablets imprinted with NPR EC 375 on one side. Packaged in light-
935 resistant bottles of 100.

936 100's (bottle): NDC 0004-6415-01.

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937 500 mg: white, oblong coated tablets imprinted with NPR EC 500 on one side.
938 Packaged in light-resistant bottles of 100.

939 100's (bottle): NDC 0004-6416-01.

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

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

944 100's (bottle): NDC 0004-6202-01.

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

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

949 100's (bottle): NDC 0004-6203-01.

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

951 Revised: September 2007

952

953 **Medication Guide**
954 **for**
955 **Non-steroidal Anti-Inflammatory Drugs (NSAIDs)**
956 **(See the end of this Medication Guide for a list of prescription NSAID**
957 **medicines.)**

958

959 **What is the most important information I should know about medicines**
960 **called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

961 **NSAID medicines may increase the chance of a heart attack or**
962 **stroke that can lead to death.** This chance increases:

- 963 • with longer use of NSAID medicines
964 • in people who have heart disease
965

966 **NSAID medicines should never be used right before or after a**
967 **heart surgery called a “coronary artery bypass graft (CABG).”**

968 **NSAID medicines can cause ulcers and bleeding in the stomach**
969 **and intestines at any time during treatment. Ulcers and bleeding:**

- 970 • can happen without warning symptoms

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971 • may cause death

972

973

974

The chance of a person getting an ulcer or bleeding increases with:

975 • taking medicines called “corticosteroids” and

976 “anticoagulants”

977 • longer use

978 • smoking

979 • drinking alcohol

980 • older age

981 • having poor health

982

983

NSAID medicines should only be used:

984 • exactly as prescribed

985 • at the lowest dose possible for your treatment

986 • for the shortest time needed

987

988 **What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

989 NSAID medicines are used to treat pain and redness, swelling, and heat
990 (inflammation) from medical conditions such as:

991 • different types of arthritis

992 • menstrual cramps and other types of short-term pain

993

994 **Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?**

995 **Do not take an NSAID medicine:**

996 • if you had an asthma attack, hives, or other allergic reaction with
997 aspirin or any other NSAID medicine

998 • for pain right before or after heart bypass surgery

999

1000 **Tell your healthcare provider:**

1001 • about all of your medical conditions.

1002 • about all of the medicines you take. NSAIDs and some other
1003 medicines can interact with each other and cause serious side
1004 effects. **Keep a list of your medicines to show to your
1005 healthcare provider and pharmacist.**

1006 • if you are pregnant. **NSAID medicines should not be used by
1007 pregnant women late in their pregnancy.**

1008 • if you are breastfeeding. **Talk to your doctor.**

1009

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1010 **What are the possible side effects of Non-Steroidal Anti-Inflammatory**
 1011 **Drugs (NSAIDs)?**

| Serious side effects include: | Other side effects include: |
|---|---|
| <ul style="list-style-type: none"> • heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma | <ul style="list-style-type: none"> • stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness |

1012 **Get emergency help right away if you have any of the following**
 1013 **symptoms:**
 1014

- | | |
|---|--|
| <ul style="list-style-type: none"> • shortness of breath or trouble breathing • chest pain • weakness in one part or side of your body | <ul style="list-style-type: none"> • slurred speech • swelling of the face or throat |
|---|--|

1015 **Stop your NSAID medicine and call your healthcare provider right away**
 1016 **if you have any of the following symptoms:**
 1017

- | | |
|---|--|
| <ul style="list-style-type: none"> • nausea • more tired or weaker than usual • itching • your skin or eyes look yellow • stomach pain • flu-like symptoms • vomit blood | <ul style="list-style-type: none"> • there is blood in your bowel movement or it is black and sticky like tar • unusual weight gain • skin rash or blisters with fever • swelling of the arms and legs, hands and feet |
|---|--|

1018 These are not all the side effects with NSAID medicines. Talk to your
 1019 healthcare provider or pharmacist for more information about NSAID
 1020

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1021 medicines. Call your doctor for medical advice about side effects. You may
1022 report side effects to FDA at 1-800-FDA-1088 or Roche at 1-800-526-6367.

1023 **Other information about Non-Steroidal Anti-Inflammatory Drugs**
1024 **(NSAIDs):**

- 1025 • Aspirin is an NSAID medicine but it does not increase the chance of a
1026 heart attack. Aspirin can cause bleeding in the brain, stomach, and
1027 intestines. Aspirin can also cause ulcers in the stomach and intestines.
- 1028 • Some of these NSAID medicines are sold in lower doses without a
1029 prescription (over-the-counter). Talk to your healthcare provider before
1030 using over-the-counter NSAIDs for more than 10 days.

1032 **NSAID medicines that need a prescription**

| Generic Name | Tradename |
|---------------------|--|
| Celecoxib | Celebrex |
| Diclofenac | Cataflam , Voltaren , Arthrotec (combined with misoprostol) |
| Diflunisal | Dolobid |
| Etodolac | Lodine , Lodine XL |
| Fenoprofen | Nalfon , Nalfon 200 |
| Flurbiprofen | Ansaid |
| Ibuprofen | Motrin , Tab-Profen , Vicoprofen * (combined with hydrocodone), Combunox (combined with oxycodone) |
| Indomethacin | Indocin , Indocin SR, Indo-Lemmon , Indomethagan |
| Ketoprofen | Oruvail |
| Ketorolac | Toradol |
| Mefenamic Acid | Ponstel |
| Meloxicam | Mobic |
| Nabumetone | Relafen |
| Naproxen | Naprosyn , Anaprox , Anaprox DS, EC-Naprosyn , Naprelan , Naprapac (copackaged with lansoprazole) |
| Oxaprozin | Daypro |
| Piroxicam | Feldene |
| Sulindac | Clinoril |
| Tolmetin | Tolectin , Tolectin DS , Tolectin 600 |

1033 *Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC)
1034 NSAID, and is usually used for less than 10 days to treat pain. The OTC

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1035 NSAID label warns that long term continuous use may increase the risk of
1036 heart attack or stroke.

1037 This Medication Guide has been approved by the U.S. Food and Drug
1038 Administration.

1039 Medication Guide Revised: July 2008

1040

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1042 owners.

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Roche Laboratories Inc.
340 Kingsland Street
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