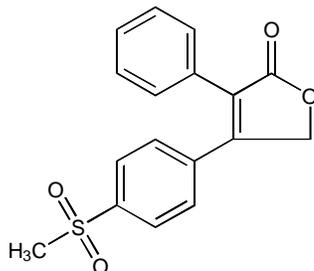


Source : USFDA

1 **VIOXX®(rofecoxib tablets and oral suspension)**

2 **DESCRIPTION**

3
4
5 VIOXX* (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-
6 2(5H)-furanone. It has the following chemical structure:



10 Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone,
11 slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol,
12 practically insoluble in octanol, and insoluble in water. The empirical formula for
13 rofecoxib is C₁₇H₁₄O₄S, and the molecular weight is 314.36.

14
15 Each tablet of VIOXX for oral administration contains either 12.5 or 25 mg of rofecoxib
16 and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose,
17 lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide.

18
19 Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the
20 following inactive ingredients: citric acid (monohydrate), sodium citrate (dihydrate),
21 sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as
22 preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

23
24 **CLINICAL PHARMACOLOGY**

25
26 **Mechanism of Action**

27 VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory,
28 analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX
29 is believed to be due to inhibition of prostaglandin synthesis, via inhibition of
30 cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not
31 inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

32
33
34
35
36 **Pharmacokinetics**

37
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38 **Absorption**

39 The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25
40 and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level
41 (C_{max}) following a single 25 mg dose were 3286(±843) ng*hr/mL and 207 (±111) ng/mL,
42 respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose
43 range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and
44 AUC, which is thought to be due to the low solubility of the drug in aqueous media. The
45 plasma concentration-time profile exhibited multiple peaks. The median time to maximal
46 concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours.
47 Individual T_{max} values in these studies ranged between 2 to 9 hours. This may not reflect
48 rate of absorption as T_{max} may occur as a secondary peak in some individuals. With
49 multiple dosing, steady state conditions are reached by Day 4. The AUC_{0-24hr} and C_{max} at
50 steady-state after multiple doses of 25 mg rofecoxib was 4018 (±1140) ng*hr/mL and 321 (±104)
51 ng/mL, respectively. The accumulation factor based on geometric means was 1.67.

52
53 VIOXX Tablets and VIOXX Oral Suspension are bioequivalent.

54

55 **Food and Antacid Effects**

56 Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption
57 (AUC) of rofecoxib when VIOXX tablets were taken with a high fat meal. The time to peak plasma
58 concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension
59 formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

60

61 There was a 13% and 8% decrease in AUC when VIOXX was administered with calcium
62 carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively.
63 There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

64

65 **Distribution**

66 Rofecoxib is approximately 87% bound to human plasma protein over the range of
67 concentrations of 0.05 to 25 µg/mL. The apparent volume of distribution at steady state
68 (V_{dss}) is approximately 91 L following a 12.5 mg dose and 86 L following a 25 mg dose.

69

70 Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain
71 barrier in rats.

72

73 **Metabolism**

74 Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal
75 metabolic products are the *cis*-dihydro and *trans*-dihydro derivatives of rofecoxib, which account for
76 nearly 56% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as the
77 glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of
78 rofecoxib and this metabolite is reversible in humans to a limited extent (<5%). These metabolites are
79 inactive as COX-1 or COX-2 inhibitors.

80

81 Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP3A activity by
82 administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of
83 general hepatic metabolic activity by administration of the non-specific inducer rifampin 600 mg daily
84 produces a 50% decrease in rofecoxib plasma concentrations. (Also see **Drug Interactions**).

85

86 ***Excretion***

87 Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged
88 drug recovered in the urine. Following a single radiolabeled dose of 125 mg,
89 approximately 72% of the dose was excreted into the urine as metabolites, and 14% in the
90 feces as unchanged drug.

91

92 The plasma clearance after 12.5 and 25 mg doses was approximately 141 and 120
93 mL/min, respectively. Higher plasma clearance was observed at doses below the
94 therapeutic range, suggesting the presence of a saturable route of metabolism (i.e, non-
95 linear elimination). The effective half-life (based on steady state levels) was approximately
96 17 hours.

97

98 **Special Populations**

99

100 ***Gender***

101 The pharmacokinetics of rofecoxib are comparable in men and women.

102

103 ***Geriatric***

104 After a single dose of 25 mg VIOXX in elderly subjects (over 65 years old) a 34%
105 increase in AUC was observed as compared to the young subjects. Dosage adjustment in
106 the elderly is not necessary; however, therapy with VIOXX should be initiated at the
107 lowest recommended dose.

108

109 ***Pediatric***

110 VIOXX has not been investigated in patients below 18 years of age.

111

112 ***Race***

113 Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC
114 of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment
115 is necessary on the basis of race.

116

117 ***Hepatic Insufficiency***

118 A pharmacokinetic study in mild (Child-Pugh score ≤ 6) hepatic insufficiency patients
119 indicated that rofecoxib AUC was similar between these patients and healthy subjects.
120 Limited data in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency
121 suggest a trend towards higher AUC (about 69%) of rofecoxib in these patients, but more
122 data are needed to evaluate pharmacokinetics in these patients. Patients with severe
123 hepatic insufficiency have not been studied.

124

125 ***Renal Insufficiency***

126 In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak
127 rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis
128 occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the
129 elimination profile of rofecoxib was unchanged. While renal insufficiency does not

130 influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is
131 not recommended at present because no safety information is available regarding the use
132 of VIOXX in these patients.

133

134 **Drug Interactions**

135

136 Also see **PRECAUTIONS – Drug Interactions.**

137

138 **General:** In human studies the potential for rofecoxib to inhibit or induce CYP 3A4
139 activity was investigated in studies using the intravenous erythromycin breath test and the
140 oral midazolam test. No significant difference in erythromycin demethylation was observed
141 with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP
142 3A4. A 30% reduction of the AUC of midazolam was observed with rofecoxib (25 mg
143 daily). This reduction is most likely due to increased first pass metabolism through
144 induction of intestinal CYP 3A4 by rofecoxib. *In vitro* studies in rat hepatocytes also
145 suggest that rofecoxib might be a mild inducer for CYP 3A4.

146

147 Drug interaction studies with rofecoxib have identified potentially significant interactions
148 with rifampin, methotrexate and warfarin. Patients receiving these agents with VIOXX
149 should be appropriately monitored. Drug interaction studies do not support the potential
150 for clinically important interactions between antacids or cimetidine with rofecoxib. Similar
151 to experience with other nonsteroidal antiinflammatory drugs (NSAIDs), studies with
152 rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of
153 rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole,
154 prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and
155 clinically important interactions have not been found .

156

157 **CLINICAL STUDIES**

158

159 **Osteoarthritis (OA)**

160 VIOXX has demonstrated significant reduction in joint pain compared to placebo.
161 VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and
162 hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled
163 approximately 3900 patients. In patients with OA, treatment with VIOXX 12.5 mg and
164 25 mg once daily resulted in improvement in patient and physician global assessments and
165 in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis
166 questionnaire, including pain, stiffness, and functional measures of OA. In six studies of
167 pain accompanying OA flare, VIOXX provided a significant reduction in pain at the first
168 determination (after one week in one study, after two weeks in the remaining five studies);
169 this continued for the duration of the studies. In all OA clinical studies, once daily
170 treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant
171 reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25
172 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID
173 and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen
174 studies were 6 week studies; the diclofenac studies were 12 month studies in which
175 patients could receive additional arthritis medication during the last 6 months.

176 **Analgesia, including Dysmenorrhea**

177 In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and
178 primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to
179 severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX
180 was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-
181 dose post-operative dental pain studies, the onset of analgesia with a single 50 mg dose of
182 VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical
183 pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX
184 once daily was effective in reducing pain. In this study, patients on VIOXX consumed a
185 significantly smaller amount of additional analgesic medication than patients treated with
186 placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and
187 placebo, respectively).

188

189 **Special Studies**

190 ***Upper Endoscopy in Patients with Osteoarthritis:***

191 Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were
192 conducted to compare the percentage of patients who developed endoscopically
193 detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400
194 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with
195 active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an
196 upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age \geq 65 years. However,
197 patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were
198 not enrolled in these studies. Patients who were 50 years of age and older with
199 osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks
200 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by
201 design.

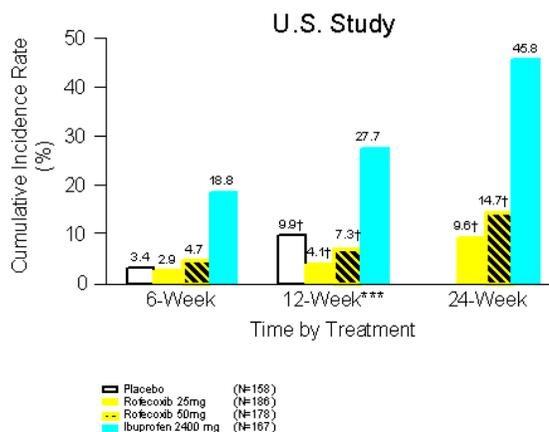
202

203 Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly
204 lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with
205 ibuprofen 2400 mg daily. However, the studies cannot rule out at least some increase in
206 the rate of endoscopic gastroduodenal ulcers when comparing VIOXX to placebo. See
207 Figures 1 and 2 and accompanying Tables for the results of these studies.

Figure 1

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers $\geq 3\text{mm}^{}$ (Intention-to-Treat)**



† p < 0.001 versus ibuprofen 2400 mg
 ** Results of analyses using a $\geq 5\text{mm}$ gastroduodenal ulcer endpoint were consistent.
 *** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

209
 210
 211
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 213
 214

TABLE 1
Endoscopic Gastroduodenal Ulcers at 12 weeks
U.S. Study

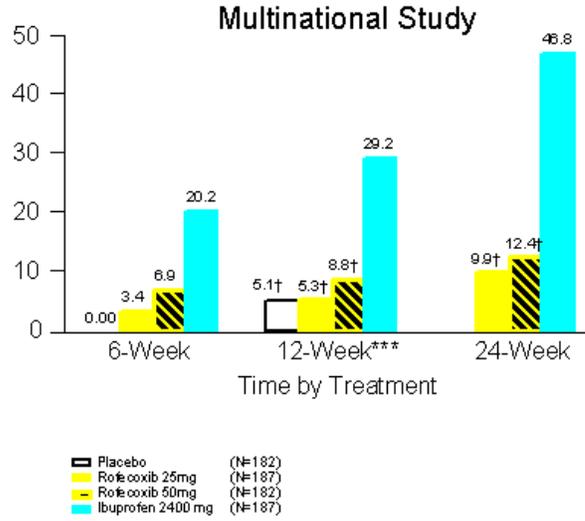
| Treatment Group | Number of Patients with Ulcer/Total Number of Patients | Cumulative Incidence Rate* | Ratio of Rates vs. Placebo | 95% CI on Ratio of Rates |
|------------------------|---|-----------------------------------|-----------------------------------|---------------------------------|
| Placebo | 11/158 | 9.9% | – | – |
| VIOXX 25 mg | 7/186 | 4.1% | 0.41 | (0.16, 1.05) |
| VIOXX 50 mg | 12/178 | 7.3% | 0.74 | (0.33, 1.64) |
| Ibuprofen | 42/167 | 27.7% | 2.79 | (1.47, 5.30) |

215 *by life table analysis
 216

Figure 2

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers $\geq 3\text{mm}^{}$ (Intention-to-Treat)**



† p < 0.001 versus ibuprofen 2400 mg
 ** Results of analyses using a $\geq 5\text{mm}$ gastroduodenal ulcer endpoint were consistent.
 *** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

218
 219
 220
 221
 222
 223

TABLE 2
Endoscopic Gastroduodenal Ulcers at 12 weeks
Multinational Study

| Treatment Group | Number of Patients with Ulcer/Total Number of Patients | Cumulative Incidence Rate* | Ratio of Rates vs. Placebo | 95% CI on Ratio of Rates |
|------------------------|---|-----------------------------------|-----------------------------------|---------------------------------|
| Placebo | 5/182 | 5.1% | – | – |
| VIOXX 25 mg | 9/187 | 5.3% | 1.04 | (0.36, 3.01) |
| VIOXX 50 mg | 15/182 | 8.8% | 1.73 | (0.65, 4.61) |
| Ibuprofen | 49/187 | 29.2% | 5.72 | (2.36, 13.89) |

224 *by life table analysis

225

226

227 The correlation between findings of endoscopic studies, and the relative incidence of
228 clinically serious upper GI events that may be observed with different products, has not
229 been fully established. Serious clinically significant upper GI bleeding has been observed
230 in patients receiving VIOXX in controlled trials, albeit infrequently (see WARNINGS –
231 Gastrointestinal [GI] Effects). Prospective, long-term studies required to compare the
232 incidence of serious, clinically significant upper GI adverse events in patients taking
233 VIOXX versus comparator NSAID products have not been performed.

234

235 ***Assessment of Fecal Occult Blood Loss in Healthy Subjects:***

236 Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily,
237 ibuprofen 2400 mg per day, and placebo was evaluated in a study utilizing ⁵¹Cr-tagged red
238 blood cells in 67 healthy males. After 4 weeks of treatment with VIOXX 25 mg daily or
239 VIOXX 50 mg daily, the increase in the amount of fecal blood loss was not statistically
240 significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per
241 day produced a statistically significant increase in fecal blood loss as compared with
242 placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this
243 finding is unknown.

244

245 ***Platelets:***

246 Multiple doses of VIOXX 12.5, 25, and up to 375 mg administered daily up to 12 days
247 had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered
248 in a single dose study with 500 or 1000 mg of VIOXX. There was no inhibition of *ex vivo*
249 arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of
250 VIOXX.

251

252 **INDICATIONS AND USAGE**

253

254 VIOXX is indicated:

255

256 For relief of the signs and symptoms of osteoarthritis.

257

258 For the management of acute pain in adults (see CLINICAL STUDIES).

259

260 For the treatment of primary dysmenorrhea.

261

262 **CONTRAINDICATIONS**

263

264 VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any
265 other component of VIOXX.

266

267 VIOXX should not be given to patients who have experienced asthma, urticaria, or
268 allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal,

269 anaphylactic-like reactions to NSAIDs have been reported in such patients (see
270 WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

271

272

273 WARNINGS

274

275 **Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation:**

276 Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the
277 stomach, small intestine or large intestine, can occur at any time, with or without warning
278 symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs).

279 Minor upper gastrointestinal problems, such as dyspepsia, are common and may also
280 occur at any time during NSAID therapy. Therefore, physicians and patients should
281 remain alert for ulceration and bleeding, even in the absence of previous GI tract
282 symptoms. Patients should be informed about the signs and/or symptoms of serious GI
283 toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring
284 has not been demonstrated, nor has it been adequately assessed. Only one in five patients
285 who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has
286 been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by
287 NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in
288 about 2-4% of patients treated for one year. These trends continue thus, increasing the
289 likelihood of developing a serious GI event at some time during the course of therapy.
290 However, even short-term therapy is not without risk.

291

292 It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL
293 STUDIES, Special Studies, *Upper Endoscopy in Patients with Osteoarthritis*). Among
294 3357 patients who received VIOXX in controlled clinical trials of 6 weeks to one year
295 duration (most were enrolled in six month or longer studies) at a daily dose of 12.5 mg to
296 50 mg, a total of 4 patients experienced a serious upper GI event, using protocol derived
297 criteria. Two patients experienced an upper GI bleed within three months (at day 62 and
298 87 respectively) (0.06%). One additional patient experienced an obstruction within six
299 months (Day 130) and the remaining patient developed an upper GI bleed within 12
300 months (Day 322) (0.12%). Approximately 23% of these 3357 patients were in studies
301 that required them to be free of ulcers at study entry. It is unclear if this study population
302 is representative of the general population. Prospective, long-term studies required to
303 compare the incidence of serious, clinically significant upper GI adverse events in patients
304 taking VIOXX vs comparator NSAID products have not been performed.

305

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

312

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

320

321 **Anaphylactoid Reactions**

322 Anaphylactoid reactions were not reported in patients receiving VIOXX in clinical trials.
323 However, as with NSAIDs in general, anaphylactoid reactions may occur in patients
324 without known prior exposure to VIOXX. VIOXX should not be given to patients with
325 the aspirin triad. This symptom complex typically occurs in asthmatic patients who
326 experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal
327 bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and
328 PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where
329 an anaphylactoid reaction occurs.

330

331 **Advanced Renal Disease**

332 No safety information is available regarding the use of VIOXX in patients with advanced
333 kidney disease. Therefore, treatment with VIOXX is not recommended in these patients.
334 If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is
335 advisable (see PRECAUTIONS - Renal Effects).

336

337 **Pregnancy**

338 In late pregnancy VIOXX should be avoided because it may cause premature closure of
339 the ductus arteriosus.

340

341 **PRECAUTIONS**

342 **General**

343 VIOXX cannot be expected to substitute for corticosteroids or to treat corticosteroid
344 insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of
345 corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should
346 have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

347

348 The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may
349 diminish the utility of these diagnostic signs in detecting infectious complications of
350 presumed noninfectious, painful conditions.

351

352 **Hepatic Effects:**

353 Borderline elevations of one or more liver tests may occur in up to 15% of patients taking
354 NSAIDs, and notable elevations of ALT or AST (approximately three or more times the
355 upper limit of normal) have been reported in approximately 1% of patients in clinical trials
356 with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or
357 may be transient with continuing therapy. Rare cases of severe hepatic reactions,

358 including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some
359 with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of
360 VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg
361 daily was comparable to the incidence observed with ibuprofen and lower than that
362 observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients
363 taking rofecoxib (12.5 or 25 mg QD) and 0.1% of patients taking placebo had notable
364 elevations of ALT or AST.

365

366 A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an
367 abnormal liver test has occurred, should be monitored carefully for evidence of the
368 development of a more severe hepatic reaction while on therapy with VIOXX. Use of
369 VIOXX is not recommended in patients with moderate or severe hepatic insufficiency (see
370 **Pharmacokinetics – Special Populations**). If clinical signs and symptoms consistent with
371 liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.),
372 VIOXX should be discontinued.

373

374 **Renal Effects:**

375 Long-term administration of NSAIDs has resulted in renal papillary necrosis and other
376 renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins
377 have a compensatory role in the maintenance of renal perfusion. In these patients,
378 administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent
379 reduction in prostaglandin formation and, secondarily, in renal blood flow, which may
380 precipitate overt renal decompensation. Patients at greatest risk of this reaction are those
381 with impaired renal function, heart failure, liver dysfunction, those taking diuretics and
382 ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by
383 recovery to the pretreatment state. Clinical trials with VIOXX at daily doses of 12.5 and
384 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with
385 comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX
386 at doses above the 12.5 to 25 mg range. (See ADVERSE REACTIONS.)

387

388 Caution should be used when initiating treatment with VIOXX in patients with
389 considerable dehydration. It is advisable to rehydrate patients first and then start therapy
390 with VIOXX. Caution is also recommended in patients with pre-existing kidney disease
391 (see WARNINGS-Advanced Renal Disease).

392

393 ***Hematological Effects:***

394 Anemia is sometimes seen in patients receiving VIOXX. In placebo-controlled trials,
395 there were no significant differences observed between VIOXX and placebo in clinical
396 reports of anemia. Patients on long-term treatment with VIOXX should have their
397 hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or
398 blood loss. VIOXX does not generally affect platelet counts, prothrombin time (PT), or
399 partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated
400 dosages (See CLINICAL STUDIES-Special Studies-Platelets).

401

402 ***Fluid Retention and Edema:***

403 Fluid retention and edema have been observed in some patients taking VIOXX (see
404 ADVERSE REACTIONS). VIOXX should be used with caution, and should be
405 introduced at the lowest recommended dose, in patients with fluid retention,
406 hypertension, or heart failure.

407

408 ***Preexisting Asthma:***

409 Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with
410 aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal.
411 Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal
412 anti-inflammatory drugs has been reported in such aspirin-sensitive patients, VIOXX
413 should not be administered to patients with this form of aspirin sensitivity and should be
414 used with caution in patients with preexisting asthma.

415

416 **Information for Patients**

417 VIOXX can cause discomfort and, rarely, more serious side effects, such as
418 gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.
419 Although serious GI tract ulcerations and bleeding can occur without warning symptoms,
420 patients should be alert for the signs and symptoms of ulcerations and bleeding, and should
421 ask for medical advice when observing any indicative signs or symptoms. Patients should
422 be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI)
423 Effects - Risk of GI Ulceration, Bleeding and Perforation).

424

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

427

428 Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g.,
429 nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like"
430 symptoms). If these occur, patients should be instructed to stop therapy and seek
431 immediate medical therapy.

432

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

435

436 In late pregnancy VIOXX should be avoided because it may cause premature closure of
437 the ductus arteriosus.

438

439 **Laboratory Tests**

440 Because serious GI tract ulcerations and bleeding can occur without warning symptoms,
441 physicians should monitor for signs or symptoms of GI bleeding.

442

443 **Drug Interactions**

444

445 ***ACE-inhibitors:*** Reports suggest that NSAIDs may diminish the antihypertensive effect of
446 Angiotensin Converting Enzyme (ACE) inhibitors. In patients with mild to moderate
447 hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril,

448 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial
449 pressure of about 3 mm Hg compared to ACE inhibitor alone. This interaction should be
450 given consideration in patients taking VIOXX concomitantly with ACE-inhibitors.

451

452 **Aspirin:** Concomitant administration of low-dose aspirin with VIOXX may result in an
453 increased rate of GI ulceration or other complications, compared to use of VIOXX alone.
454 At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of
455 low-dose (81 mg once daily) aspirin, as assessed by *ex vivo* platelet aggregation and serum
456 TXB₂ generation in clotting blood. VIOXX is not a substitute for aspirin for
457 cardiovascular prophylaxis.

458

459 **Cimetidine:** Co-administration with high doses of cimetidine [800 mg twice daily]
460 increased the C_{max} of rofecoxib by 21%, the AUC_{0-120hr} by 23% and the t_{1/2} by 15%. These
461 small changes are not clinically significant and no dose adjustment is necessary.

462

463 **Digoxin:** Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration
464 profile or renal elimination of digoxin after a single 0.5 mg oral dose.

465

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

469

470 **Ketoconazole:** Ketoconazole 400 mg daily did not have any clinically important effect on
471 the pharmacokinetics of rofecoxib.

472

473 **Lithium:** NSAIDs have produced an elevation of plasma lithium levels and a reduction in
474 renal lithium clearance. Thus, when VIOXX and lithium are administered concurrently,
475 subjects should be observed carefully for signs of lithium toxicity.

476

477 **Methotrexate:** VIOXX 75 mg administered once daily for 10 days increased plasma
478 concentrations by 23% as measured by AUC_{0-24 hr} in patients receiving methotrexate 7.5 to
479 15 mg/week for rheumatoid arthritis. An equivalent magnitude of reduction in
480 methotrexate renal clearance was observed. At 24 hours postdose, a similar proportion of
481 patients treated with methotrexate alone (94%) and subsequently treated with
482 methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma
483 concentrations below the measurable limit (5 ng/mL). The effects of the recommended
484 doses for osteoarthritis (12.5 and 25 mg) of VIOXX on plasma methotrexate levels are
485 unknown. Standard monitoring of methotrexate-related toxicity should be continued if
486 VIOXX and methotrexate are administered concomitantly.

487

488 **Oral Contraceptives:** Rofecoxib did not have any clinically important effect on the
489 pharmacokinetics of ethinyl estradiol and norethindrone.

490

491 **Prednisone/prednisolone:** Rofecoxib did not have any clinically important effect on the
492 pharmacokinetics of prednisolone or prednisone.

493

494 **Rifampin:** Co-administration of VIOXX with rifampin 600mg daily, a potent inducer of
495 hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma
496 concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered
497 for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers
498 of hepatic metabolism.

499

500 **Warfarin:** Prothrombin time (measured as INR) increased in both single and multiple dose
501 cross-over studies in healthy individuals receiving both warfarin and rofecoxib. In a 21 day
502 multiple dose study in healthy individuals stabilized on warfarin (2 to 8.5 mg daily),
503 administration of rofecoxib 25 mg QD was associated with mean increases in INR of
504 approximately 8% (range of INR on warfarin alone, 1.1 to 2.2; range of INR on warfarin
505 plus rofecoxib, 1.2 to 2.4). Somewhat greater mean increases in INR of approximately
506 11% (range of maximum INR on warfarin alone, 1.5 to 2.7; range of maximum INR on
507 warfarin plus rofecoxib, 1.6 to 4.4) were also seen in a single dose PK screening study
508 using a 30 mg dose of warfarin and 50 mg of rofecoxib. Standard monitoring of INR
509 values should be conducted when therapy with VIOXX is initiated or changed, particularly
510 in the first few days, in patients receiving warfarin or similar agents.

511

512 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

513 Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (male) and 60
514 mg/kg (female) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily
515 based on AUC₀₋₂₄) and in male and female rats given oral doses up to 8 mg/kg
516 (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on AUC₀₋₂₄)
517 for two years.

518

519 Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis
520 assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO)
521 cells, in an *in vitro* and an *in vivo* alkaline elution assay, or in an *in vivo* chromosomal
522 aberration test in mouse bone marrow.

523

524 Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg
525 (approximately 20- and 7-fold human exposure at 25 and 50 mg daily based on the AUC₀₋₂₄)
526 and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg
527 (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on AUC₀₋₂₄).

528

529 **Pregnancy:**

530 **Teratogenic effects:** Pregnancy Category C. Rofecoxib was not teratogenic in rats at
531 doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50
532 mg daily based on AUC₀₋₂₄). There was a slight, non-statistically significant increase in the
533 overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day
534 (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on AUC₀₋₂₄).
535 There are no studies in pregnant women. VIOXX should be used during pregnancy only if
536 the potential benefit justifies the potential risk to the fetus.

537

538 ***Nonteratogenic effects:*** Rofecoxib produced peri-implantation and post-implantation
539 losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥ 10 and ≥ 75
540 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1 -fold [rabbits]
541 human exposure based on the AUC₀₋₂₄ at 25 and 50 mg daily). These changes are
542 expected with inhibition of prostaglandin synthesis and are not the result of permanent
543 alteration of female reproductive function. There was an increase in the incidence of
544 postnatal pup mortality in rats at ≥ 5 mg/kg/day (approximately 5- and 2-fold human
545 exposure at 25 and 50 mg daily based on AUC₀₋₂₄). In studies in pregnant rats
546 administered single doses of rofecoxib, there was a treatment-related decrease in the
547 diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is
548 approximately 2- and <1 -fold human exposure at 25 or 50 mg daily based on AUC₀₋₂₄). As
549 with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third
550 trimester of pregnancy should be avoided.

551

552 ***Labor and delivery:*** Rofecoxib produced no evidence of significantly delayed labor or
553 parturition in females at doses < 15 mg/kg in rats (approximately 10- and 3-fold human
554 exposure as measured by the AUC₀₋₂₄ at 25 and 50 mg). The effects of VIOXX on labor
555 and delivery in pregnant women are unknown.

556

557 ***Nursing mothers:*** Rofecoxib is excreted in the milk of lactating rats at concentrations
558 similar to those in plasma. There was an increase in pup mortality and a decrease in pup
559 body weight following exposure of pups to milk from dams administered VIOXX during
560 lactation. The dose tested represents approximately 18- and 6-fold human exposure at 25
561 and 50 mg based on AUC₀₋₂₄. It is not known whether this drug is excreted in human milk.
562 Because many drugs are excreted in human milk and because of the potential for serious
563 adverse reactions in nursing infants from VIOXX, a decision should be made whether to
564 discontinue nursing or to discontinue the drug, taking into account the importance of the
565 drug to the mother.

566

567 **Pediatric Use**

568 Safety and effectiveness in pediatric patients below the age of 18 years have not been
569 evaluated.

570

571 **Geriatric Use**

572 Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of
573 age or older (this included 460 who were 75 years or older. No substantial differences in
574 safety and effectiveness were observed between these subjects and younger subjects.
575 Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in
576 the elderly is not necessary; however, therapy with VIOXX should be initiated at the
577 lowest recommended dose.

578

579 In one of these studies (a six-week, double-blind, randomized clinical trial), VIOXX 12.5
580 or 25 mg once daily was administered to 174 osteoarthritis patients ≥ 80 years of age. The
581 safety profile in this elderly population was similar to that of younger patients treated with
582 VIOXX.

583

584

585 **ADVERSE REACTIONS**

586

587 *Osteoarthritis*

588

589 Approximately 3600 patients with osteoarthritis were treated with VIOXX; approximately
590 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for
591 one year or longer. The following table of adverse experiences lists all adverse events
592 regardless of causality, occurring in at least 2% of patients receiving VIOXX in nine
593 controlled studies of 6 weeks to 6 months duration conducted in patients with OA at the
594 therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or
595 positive control group.

Clinical Adverse Experiences occurring in
 $\geq 2.0\%$ of Patients Treated with VIOXX

| | Placebo (N = 783) | VIOXX 12.5 or 25 mg daily (N = 2829) | Ibuprofen 2400 mg daily (N = 847) | Diclofenac 150 mg daily (N = 498) |
|---|----------------------|--|--|--|
| Body As A Whole/Site Unspecified | | | | |
| Abdominal Pain | 4.1 | 3.4 | 4.6 | 5.8 |
| Asthenia/Fatigue | 1.0 | 2.2 | 2.0 | 2.6 |
| Dizziness | 2.2 | 3.0 | 2.7 | 3.4 |
| Influenza-Like Disease | 3.1 | 2.9 | 1.5 | 3.2 |
| Lower Extremity Edema | 1.1 | 3.7 | 3.8 | 3.4 |
| Upper Respiratory Infection | 7.8 | 8.5 | 5.8 | 8.2 |
| Cardiovascular System | | | | |
| Hypertension | 1.3 | 3.5 | 3.0 | 1.6 |
| Digestive System | | | | |
| Diarrhea | 6.8 | 6.5 | 7.1 | 10.6 |
| Dyspepsia | 2.7 | 3.5 | 4.7 | 4.0 |
| Epigastric Discomfort | 2.8 | 3.8 | 9.2 | 5.4 |
| Heartburn | 3.6 | 4.2 | 5.2 | 4.6 |
| Nausea | 2.9 | 5.2 | 7.1 | 7.4 |
| Eyes, Ears, Nose, And Throat | | | | |
| Sinusitis | 2.0 | 2.7 | 1.8 | 2.4 |
| Musculoskeletal System | | | | |
| Back Pain | 1.9 | 2.5 | 1.4 | 2.8 |
| Nervous System | | | | |
| Headache | 7.5 | 4.7 | 6.1 | 8.0 |
| Respiratory System | | | | |
| Bronchitis | 0.8 | 2.0 | 1.4 | 3.2 |
| Urogenital System | | | | |
| Urinary Tract Infection | 2.7 | 2.8 | 2.5 | 3.6 |

597

598 The general safety profile of VIOXX 50 mg QD in OA clinical trials up to 6 months (476
599 patients) was similar to that of VIOXX at the recommended OA doses of 12.5 and 25 mg
600 QD, except for a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric
601 pain, heartburn, nausea and vomiting), lower extremity edema (6.3%) and hypertension
602 (8.2%).

603

604 In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9%
605 of patients treated with VIOXX regardless of causality:

606

607 **Body as a Whole:** abdominal distension, abdominal tenderness, abscess, chest pain, chills,
608 contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection,
609 infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope,
610 trauma, upper extremity edema, viral syndrome.

611

612 **Cardiovascular System:** angina pectoris, atrial fibrillation, bradycardia, hematoma,
613 irregular heart beat, palpitation, premature ventricular contraction, tachycardia, venous
614 insufficiency.

615

616 **Digestive System:** acid reflux, aphthous stomatitis, constipation, dental caries, dental
617 pain, digestive gas symptoms, dry mouth, duodenal disorder, dysgeusia, esophagitis,
618 flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids,
619 infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

620

621 **Eyes, Ears, Nose and Throat:** allergic rhinitis, blurred vision, cerumen impaction,
622 conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion,
623 ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

624

625 **Immune System:** allergy, insect bite reaction

626

627 **Metabolism And Nutrition:** appetite change, hypercholesterolemia, weight gain

628

629 **Musculoskeletal System:** ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage
630 trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness,
631 musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis,
632 traumatic arthropathy, wrist fracture

633

634 **Nervous System:** hypesthesia, insomnia, median nerve neuropathy, migraine, muscular
635 spasm, paresthesia, sciatica, somnolence, vertigo

636

637 **Psychiatric Disorder:** anxiety, depression, mental acuity decreased

638

639 **Respiratory System:** asthma, cough, dyspnea, pneumonia, pulmonary congestion,
640 respiratory infection

641

642 **Skin And Skin Appendages:** abrasion, alopecia, atopic dermatitis, basal cell carcinoma,
643 blister, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail unit disorder,
644 perspiration, pruritus, rash, skin erythema, urticaria, xerosis

645

646 **Urogenital System:** breast mass, cystitis, dysuria, menopausal symptoms, menstrual
647 disorder, nocturia, urinary retention, vaginitis

648

649 **Other serious adverse reactions which occur rarely (<0.1%), regardless of causality:**

650 The following serious adverse events have occurred rarely in patients taking VIOXX:

651

652 **Cardiovascular:** cerebrovascular accident, congestive heart failure, deep venous
653 thrombosis, myocardial infarction, pulmonary embolism, transient ischemic attack,
654 unstable angina

655

656 **Gastrointestinal:** colitis, colonic malignant neoplasm, cholecystitis, duodenal ulcer,
657 gastrointestinal bleeding, intestinal obstruction, pancreatitis

658

659 **Hemic and lymphatic:** lymphoma

660

661 **Urogenital:** breast malignant neoplasm, prostatic malignant neoplasm, urolithiasis

662

663 In 1-year controlled clinical trials and in extension studies for up to 86 weeks
664 (approximately 800 patients treated with VIOXX for one year or longer), the adverse
665 experience profile was qualitatively similar to that observed in studies of shorter duration.

666

667 *Analgesia, including primary dysmenorrhea*

668 Approximately one thousand patients were treated with VIOXX in analgesia studies. All
669 patients in post-dental surgery pain studies received only a single dose of study
670 medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses
671 of VIOXX, and those in the post-orthopedic surgery pain study were prescribed 5 daily
672 doses of VIOXX.

673

674 The adverse experience profile in the analgesia studies was generally similar to those
675 reported in the osteoarthritis studies. The following additional adverse experience, which
676 occurred at an incidence of at least 2% of patients treated with VIOXX, was observed in
677 the post-dental pain surgery studies: post-dental extraction alveolitis (dry socket).

678

679 In 110 patients treated with VIOXX (average age approximately 65 years) in the post-
680 orthopedic surgery pain study, the most commonly reported adverse experiences were
681 constipation, fever, and nausea.

682

683 **OVERDOSAGE**

684 No overdoses of VIOXX were reported during clinical trials. Administration of single
685 doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for
686 14 days to 75 healthy volunteers did not result in serious toxicity.

687
688 In the event of overdose, it is reasonable to employ the usual supportive measures, e.g.,
689 remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring,
690 and institute supportive therapy, if required.

691
692 Rofecoxib is not removed by hemodialysis; it is not known whether rofecoxib is removed
693 by peritoneal dialysis.

694

695 **DOSAGE AND ADMINISTRATION**

696 VIOXX is administered orally. The lowest dose of VIOXX should be sought for each
697 patient.

698

699 *Osteoarthritis*

700 The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may
701 receive additional benefit by increasing the dose to 25 mg once daily. The maximum
702 recommended daily dose is 25 mg.

703

704 *Management of Acute Pain and Treatment of Primary Dysmenorrhea*

705 The recommended initial dose of VIOXX is 50 mg once daily. Subsequent doses should
706 be 50 mg once daily as needed. Use of VIOXX for more than 5 days in management of
707 pain has not been studied (See CLINICAL STUDIES, *Analgesia, including primary*
708 *dysmenorrhea.*)

709

710 VIOXX tablets may be taken with or without food.

711

712 *Oral Suspension*

713 VIOXX Oral Suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX
714 Tablets 12.5 or 25 mg, respectively, in any of the above indications. Shake before using.

715

716 **HOW SUPPLIED**

717 No. 3810 – Tablets VIOXX, 12.5 mg, are cream/off-white, round, shallow cup tablets
718 engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

719 **NDC 0006-0074-31** unit of use bottles of 30

720 **NDC 0006-0074-54** unit of use bottles of 90

721 **NDC 0006-0074-28** unit dose packages of 100

722 **NDC 0006-0074-68** bottles of 100

723 **NDC 0006-0074-82** bottles of 1000

724 **NDC 0006-0074-80** bottles of 8000.

725

726 No. 3811 – Tablets VIOXX, 25 mg, are yellow, round, tablets engraved MRK 110 on one
727 side and VIOXX on the other. They are supplied as follows:

728 **NDC 0006-0110-31** unit of use bottles of 30

729 **NDC 0006-0110-54** unit of use bottles of 90

730 **NDC 0006-0110-28** unit dose packages of 100

731 **NDC 0006-0110-68** bottles of 100

732 **NDC 0006-0110-82** bottles of 1000

733 **NDC 0006-0110-80** bottles of 8000.

734

735 No. 3784 – Oral Suspension VIOXX, 12.5 mg/5 mL is an opaque, white to faint yellow
736 suspension with a strawberry flavor that is easily resuspended upon shaking.

737 **NDC 0006-3784-64** unit of use bottles containing 150 mL (12.5 mg/5 mL).

738

739 No. 3785 – Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow
740 suspension with a strawberry flavor that is easily resuspended upon shaking.

741 **NDC 0006-3785-64** unit of use bottles containing 150 mL (25 mg/5 mL).

742

743 *Storage*

744 *VIOXX Tablets:*

745 Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP
746 Controlled Room Temperature.]

747

748 *VIOXX Oral Suspension:*

749 Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP
750 Controlled Room Temperature.]

751

752 Rx only.

753

754

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