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6 **CELEBREX<sup>®</sup>**  
7 celecoxib capsules  
8

9 **Cardiovascular Risk**

- 10 • CELEBREX may cause an increased risk of serious cardiovascular thrombotic  
11 events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may  
12 have a similar risk. This risk may increase with duration of use. Patients with  
13 cardiovascular disease or risk factors for cardiovascular disease may be at greater  
14 risk (see **WARNINGS** and **CLINICAL STUDIES**).
- 15
- 16 • CELEBREX is contraindicated for the treatment of peri-operative pain in the setting  
17 of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).
- 18

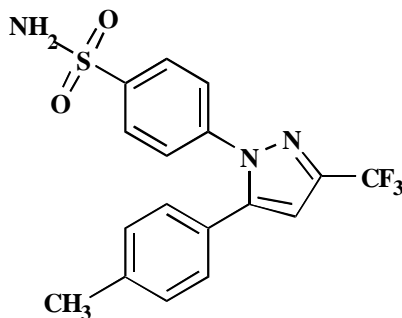
19 **Gastrointestinal Risk**

- 20 • NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal  
21 adverse events including bleeding, ulceration, and perforation of the stomach or  
22 intestines, which can be fatal. These events can occur at any time during use and  
23 without warning symptoms. Elderly patients are at greater risk for serious  
24 gastrointestinal events (see **WARNINGS**).
- 25

26  
27 **DESCRIPTION**

28  
29 CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-  
30 (trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted  
31 pyrazole. It has the following chemical structure:

32



33  
34  
35  
36 The empirical formula for celecoxib is C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S, and the molecular weight is  
37 381.38.  
38

39 CELEBREX oral capsules contain either 50 mg, 100 mg, 200 mg or 400 mg of  
40 celecoxib.

41  
42 The inactive ingredients in CELEBREX capsules include: croscarmellose sodium,  
43 edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone and sodium  
44 lauryl sulfate.

## 45 46 **CLINICAL PHARMACOLOGY**

47  
48 **Mechanism of Action:** CELEBREX is a nonsteroidal anti-inflammatory drug that exhibits  
49 anti-inflammatory, analgesic, and antipyretic activities in animal models. The  
50 mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin  
51 synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic  
52 concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1)  
53 isoenzyme. In animal colon tumor models, celecoxib reduced the incidence and  
54 multiplicity of tumors.

### 55 56 **Platelets**

57 In clinical trials using normal volunteers, CELEBREX at single doses up to 800 mg and  
58 multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended  
59 therapeutic doses) had no effect on reduction of platelet aggregation or increase in  
60 bleeding time. Because of its lack of platelet effects, CELEBREX is not a substitute for  
61 aspirin for cardiovascular prophylaxis. It is not known if there are any effects of  
62 CELEBREX on platelets that may contribute to the increased risk of serious cardiovascular  
63 thrombotic adverse events associated with the use of CELEBREX.

### 64 65 **Fluid Retention**

66 Inhibition of PGE2 synthesis may lead to sodium and water retention through increased  
67 reabsorption in the renal medullary thick ascending loop of Henle and perhaps other  
68 segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water  
69 reabsorption by counteracting the action of antidiuretic hormone.

### 70 71 **Pharmacokinetics:**

#### 72 ***Absorption***

73 Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under  
74 fasting conditions, both peak plasma levels ( $C_{max}$ ) and area under the curve (AUC) are  
75 roughly dose proportional up to 200 mg BID; at higher doses there are less than  
76 proportional increases in  $C_{max}$  and AUC (see ***Food Effects***). Absolute bioavailability  
77 studies have not been conducted. With multiple dosing, steady state conditions are  
78 reached on or before Day 5.

79  
80 The pharmacokinetic parameters of celecoxib in a group of healthy subjects are  
81 shown in Table 1.

83  
84  
85  
86

**Table 1**  
**Summary of Single Dose (200 mg) Disposition**  
**Kinetics of Celecoxib in Healthy Subjects<sup>1</sup>**

Mean (%CV) PK Parameter Values				
<b>C<sub>max</sub>, ng/mL</b>	<b>T<sub>max</sub>, hr</b>	<b>Effective t<sub>1/2</sub>, hr</b>	<b>V<sub>ss</sub>/F, L</b>	<b>CL/F, L/hr</b>
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

87 <sup>1</sup>Subjects under fasting conditions (n=36, 19-52 yrs.)

88

### 89 ***Food Effects***

90 When CELEBREX capsules were taken with a high fat meal, peak plasma levels were  
91 delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%.  
92 Under fasting conditions, at doses above 200 mg, there is less than a proportional  
93 increase in C<sub>max</sub> and AUC, which is thought to be due to the low solubility of the drug in  
94 aqueous media. Coadministration of CELEBREX with an aluminum- and magnesium-  
95 containing antacid resulted in a reduction in plasma celecoxib concentrations with a  
96 decrease of 37% in C<sub>max</sub> and 10% in AUC. CELEBREX, at doses up to 200 mg BID can be  
97 administered without regard to timing of meals. Higher doses (400 mg BID) should be  
98 administered with food to improve absorption.

99

100 In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was  
101 equivalent when celecoxib was administered as intact capsule or capsule contents  
102 sprinkled on applesauce. There were no significant alterations in C<sub>max</sub>, T<sub>max</sub> or T<sub>1/2</sub> after  
103 administration of capsule contents on applesauce.

104

### 105 ***Distribution***

106 In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose  
107 range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser  
108 extent,  $\alpha_1$ -acid glycoprotein. The apparent volume of distribution at steady state (V<sub>ss</sub>/F)  
109 is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is  
110 not preferentially bound to red blood cells.

111

### 112 ***Metabolism***

113 Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three  
114 metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide  
115 conjugate, have been identified in human plasma. These metabolites are inactive as  
116 COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor  
117 metabolizers based on a previous history should be administered celecoxib with caution  
118 as they may have abnormally high plasma levels due to reduced metabolic clearance.

119

### 120 ***Excretion***

121 Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%)  
122 unchanged drug recovered in the urine and feces. Following a single oral dose of  
123 radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was  
124 excreted into the urine. The primary metabolite in both urine and feces was the  
125 carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also  
126 appearing in the urine. It appears that the low solubility of the drug prolongs the

127 absorption process making terminal half-life ( $t_{1/2}$ ) determinations more variable. The  
128 effective half-life is approximately 11 hours under fasted conditions. The apparent  
129 plasma clearance (CL/F) is about 500 mL/min.

### 131 **Special Populations**

132  
133 **Geriatric:** At steady state, elderly subjects (over 65 years old) had a 40% higher  $C_{max}$  and  
134 a 50% higher AUC compared to the young subjects. In elderly females, celecoxib  $C_{max}$   
135 and AUC are higher than those for elderly males, but these increases are predominantly  
136 due to lower body weight in elderly females. Dose adjustment in the elderly is not  
137 generally necessary. However, for patients of less than 50 kg in body weight, initiate  
138 therapy at the lowest recommended dose.

139  
140 **Pediatric:** The steady state pharmacokinetics of celecoxib administered as an  
141 investigational oral suspension was evaluated in 152 juvenile rheumatoid arthritis (JRA)  
142 patients 2 years to 17 years of age weighing  $\geq 10$  kg with pauciarticular or polyarticular  
143 course JRA and in patients with systemic onset JRA. Population pharmacokinetic  
144 analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib  
145 increases less than proportionally to increasing weight, with 10 kg and 25 kg patients  
146 predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg  
147 adult RA patient.

148  
149 Twice-daily administration of 50 mg capsules to JRA patients weighing  $\geq 12$  to  $\leq 25$  kg  
150 and 100 mg capsules to JRA patients weighing  $> 25$  kg should achieve plasma  
151 concentrations similar to those observed in a clinical trial that demonstrated the non-  
152 inferiority of celecoxib to naproxen 7.5 mg/kg twice daily (see DOSAGE AND  
153 ADMINISTRATION). Celecoxib has not been studied in JRA patients under the age of  
154 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks.

155  
156 **Race:** Meta-analysis of pharmacokinetic studies has suggested an approximately 40%  
157 higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical  
158 significance of this finding is unknown.

159  
160 **Hepatic Insufficiency:** A pharmacokinetic study in subjects with mild (Child-Pugh  
161 Class A) and moderate (Child-Pugh Class B) hepatic impairment has shown that steady-  
162 state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in  
163 healthy control subjects. Therefore, the daily recommended dose of CELEBREX capsules  
164 should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B)  
165 hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class C) have  
166 not been studied. The use of CELEBREX in patients with severe hepatic impairment is not  
167 recommended (see **DOSAGE AND ADMINISTRATION**).

168  
169 **Renal Insufficiency:** In a cross-study comparison, celecoxib AUC was approximately  
170 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that  
171 seen in subjects with normal renal function. No significant relationship was found  
172 between GFR and celecoxib clearance. Patients with severe renal insufficiency have not

173 been studied. Similar to other NSAIDs, CELEBREX is not recommended in patients with  
174 severe renal insufficiency (see **WARNINGS – Advanced Renal Disease**).

175  
176 **Drug Interactions**

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

178  
179 **General:** Significant interactions may occur when celecoxib is administered together  
180 with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an  
181 inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

182  
183 Clinical studies with celecoxib have identified potentially significant interactions with  
184 fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs  
185 (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors.  
186 The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide,  
187 ketoconazole, methotrexate, phenytoin, and tolbutamide have been studied *in vivo* and  
188 clinically important interactions have not been found.

189  
190 **CLINICAL STUDIES**

191  
192 **Osteoarthritis (OA):** CELEBREX has demonstrated significant reduction in joint pain  
193 compared to placebo. CELEBREX was evaluated for treatment of the signs and the  
194 symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of  
195 up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or  
196 200 mg QD resulted in improvement in WOMAC (Western Ontario and McMaster  
197 Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures  
198 in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100  
199 mg BID and 200 mg BID provided significant reduction of pain within 24-48 hours of  
200 initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of  
201 CELEBREX was shown to be similar to that of naproxen 500 mg BID. Doses of 200 mg  
202 BID provided no additional benefit above that seen with 100 mg BID. A total daily dose  
203 of 200 mg has been shown to be equally effective whether administered as 100 mg BID  
204 or 200 mg QD.

205  
206 **Rheumatoid Arthritis (RA):** CELEBREX has demonstrated significant reduction in joint  
207 tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for  
208 treatment of the signs and symptoms of RA in placebo- and active-controlled clinical  
209 trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in  
210 these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and  
211 functional measures in RA. CELEBREX doses of 100 mg BID and 200 mg BID were  
212 similar in effectiveness and both were comparable to naproxen 500 mg BID.

213  
214 Although CELEBREX 100 mg BID and 200 mg BID provided similar overall  
215 effectiveness, some patients derived additional benefit from the 200 mg BID dose. Doses  
216 of 400 mg BID provided no additional benefit above that seen with 100-200 mg BID.

219 **Juvenile Rheumatoid Arthritis (JRA):** In a 12-week, randomized, double-blind active-  
220 controlled, parallel-group, multicenter, non-inferiority study, patients from 2 years to 17  
221 years of age with pauciarticular, polyarticular course JRA or systemic onset JRA (with  
222 currently inactive systemic features), received one of the following treatments: celecoxib  
223 3 mg/kg (to a maximum of 150 mg) twice daily; celecoxib 6 mg/kg (to a maximum of  
224 300 mg) twice daily; or naproxen 7.5 mg/kg (to a maximum of 500 mg) twice daily. The  
225 response rates were based upon the JRA Definition of Improvement greater than or equal  
226 to 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and  
227 functional measures of JRA. The JRA DOI 30 response rates at week 12 were 69%, 80%  
228 and 67% in the celecoxib 3 mg/kg BID, celecoxib 6 mg/kg BID, and naproxen 7.5 mg/kg  
229 BID treatment groups, respectively.

230

231 The efficacy and safety of CELEBREX for JRA have not been studied beyond six months.  
232 The long-term cardiovascular toxicity in children exposed to CELEBREX has not been  
233 evaluated and it is unknown if the long-term risk may be similar to that seen in adults  
234 exposed to CELEBREX or other COX-2 selective and non-selective NSAIDS. (see **Boxed**  
235 **Warning, WARNINGS, and PRECAUTIONS**)

236

237 **Analgesia, including primary dysmenorrhea:** In acute analgesic models of post-oral  
238 surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX  
239 relieved pain that was rated by patients as moderate to severe. Single doses (see  
240 **DOSAGE AND ADMINISTRATION**) of CELEBREX provided pain relief within 60  
241 minutes.

242

243 **Ankylosing Spondylitis (AS):** CELEBREX was evaluated in AS patients in two placebo-  
244 and active-controlled clinical trials of 6 and 12 weeks duration. CELEBREX at doses of  
245 100 mg BID, 200 mg QD and 400 mg QD was shown to be statistically superior to  
246 placebo in these studies for all three co-primary efficacy measures assessing global pain  
247 intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale) and  
248 functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week  
249 study, there was no difference in the extent of improvement between the 200 mg and 400  
250 mg celecoxib doses in a comparison of mean change from baseline, but there was a  
251 greater percentage of patients who responded to celecoxib 400 mg, 53%, than to  
252 celecoxib 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response  
253 criteria (ASAS 20). The ASAS 20 defines a responder as improvement from baseline of  
254 at least 20% and an absolute improvement of at least 10 mm, on a 0 to 100 mm scale, in  
255 at least three of the four following domains: patient global, pain, Bath Ankylosing  
256 Spondylitis Functional Index, and inflammation. The responder analysis also  
257 demonstrated no change in the responder rates beyond 6 weeks.

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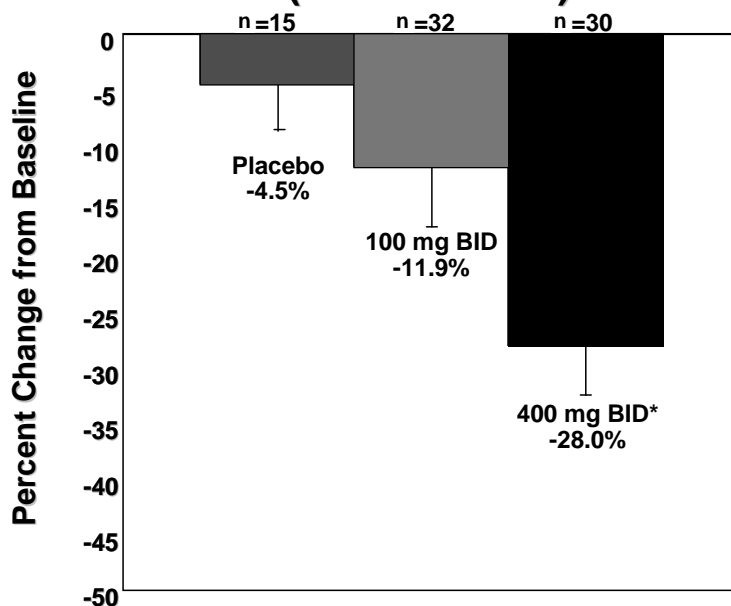
259

260 **Familial Adenomatous Polyposis (FAP):** CELEBREX was evaluated to reduce the  
261 number of adenomatous colorectal polyps. A randomized double-blind placebo-  
262 controlled study was conducted in patients with FAP. The study population included 58  
263 patients with a prior subtotal or total colectomy and 25 patients with an intact colon.  
264 Thirteen patients had the attenuated FAP phenotype.

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One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for CELEBREX 400 mg BID, 12% for CELEBREX 100 mg BID and 5% for placebo. The reduction in polyps observed with CELEBREX 400 mg BID was statistically superior to placebo at the six-month timepoint ( $p=0.003$ ). (See Figure 1.)

**Figure 1**  
**Percent Change from Baseline in**  
**Number of Colorectal Polyps**  
**(FAP Patients)**



\*  $p=0.003$  versus placebo

273  
274

### Special Studies

#### *Celecoxib Long-Term Arthritis Safety Study (CLASS)*

277 The Celecoxib Long-Term Arthritis Safety Study (CLASS) was a prospective long-term  
278 safety outcome study conducted postmarketing in approximately 5,800 OA patients and  
279 2,200 RA patients. Patients received CELEBREX 400 mg BID (4-fold and 2-fold the  
280 recommended OA and RA doses, respectively, and the approved dose for FAP),  
281 ibuprofen 800 mg TID or diclofenac 75 mg BID (common therapeutic doses). Median  
282 exposures for CELEBREX ( $n = 3,987$ ) and diclofenac ( $n = 1,996$ ) were 9 months while  
283 ibuprofen ( $n = 1,985$ ) was 6 months. The primary endpoint of this outcome study was  
284 the incidence of *complicated ulcers* (gastrointestinal bleeding, perforation or  
285 obstruction). Patients were allowed to take concomitant low-dose ( $\leq 325$  mg/day) aspirin  
286 (ASA) for cardiovascular prophylaxis (ASA subgroups: CELEBREX,  $n = 882$ ; diclofenac,  
287  $n = 445$ ; ibuprofen,  $n = 412$ ). Differences in the incidence of *complicated ulcers* between

288 CELEBREX and the combined group of ibuprofen and diclofenac were not statistically  
289 significant.

290

291 Those patients on CELEBREX and concomitant low-dose ASA (N=882) experienced 4-  
292 fold higher rates of *complicated ulcers* compared to those not on ASA (N=3105). The  
293 Kaplan Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those  
294 on low dose ASA and those not on ASA, respectively (see **WARNINGS —**  
295 **Gastrointestinal (GI) Effects-Risk of GI Ulceration, Bleeding, and Perforation**).

296

297 The estimated cumulative rates at 9 months of *complicated and symptomatic ulcers* for  
298 patients treated with CELEBREX 400 mg BID are described in Table 2. Table 2 also  
299 displays results for patients less than or greater than 65 years of age. The difference in  
300 rates between CELEBREX alone and CELEBREX with ASA groups may be due to the higher  
301 risk for GI events in ASA users.

302

303

**Table 2**

304 *Complicated and Symptomatic Ulcer Rates in Patients Taking CELEBREX 400 mg BID (Kaplan-Meier*  
305 *Rates at 9 months [%]) Based on Risk Factors*

306

307

*Complicated and Symptomatic  
Ulcer Rates*

308

309 All Patients

310 Celebrex alone (n=3105) 0.78

311 Celebrex with ASA (n=882) 2.19

312

313 Patients <65 Years

314 Celebrex alone (n=2025) 0.47

315 Celebrex with ASA (n=403) 1.26

316

317 Patients ≥65 Years

318 Celebrex alone (n=1080) 1.40

319 Celebrex with ASA (n=479) 3.06

320

321 In a small number of patients with a history of ulcer disease, the *complicated and*  
322 *symptomatic ulcer* rates in patients taking CELEBREX alone or CELEBREX with ASA were,  
323 respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be  
324 expected in patients with a prior history of ulcer disease (see **WARNINGS –**  
325 **Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation** and  
326 **ADVERSE REACTIONS – Safety Data from CLASS Study – Hematological**  
327 **Events**).

328

329 Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier  
330 cumulative rates for investigator-reported serious cardiovascular thromboembolic  
331 adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable  
332 angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated  
333 no differences between the CELEBREX, diclofenac, or ibuprofen treatment groups. The



334 cumulative rates in all patients at nine months for CELEBREX, diclofenac, and ibuprofen  
335 were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at  
336 nine months in each of the three treatment groups were less than 1%. The cumulative  
337 rates for myocardial infarction in non-ASA users at nine months in each of the three  
338 treatment groups were less than 0.2%. There was no placebo group in the CLASS trial,  
339 which limits the ability to determine whether the three drugs tested had no increased risk  
340 of CV events or if they all increased the risk to a similar degree.

341

### 342 *Adenomatous Polyp Prevention Studies*

343 Cardiovascular safety was evaluated in two randomized, double-blind, placebo-  
344 controlled, three-year studies involving patients with Sporadic Adenomatous Polyps  
345 treated with CELEBREX. The first of these studies was the APC (Prevention of Sporadic  
346 Colorectal Adenomas with Celecoxib) study, which compared CELEBREX 400 mg twice  
347 daily (N=671) and CELEBREX 200 mg twice daily (N=685) to placebo (N=679).  
348 Preliminary safety information from this trial demonstrated a dose-related increase in  
349 serious cardiovascular events (mainly myocardial infarction [MI]) at CELEBREX doses of  
350 200 mg and 400 mg twice daily compared to placebo). The cumulative rates of serious  
351 cardiovascular thrombotic events began to differ between the CELEBREX treatment groups  
352 and placebo after approximately one year of treatment. There were 2.8 to 3.1 years of  
353 follow-up in the APC trial except those patients who died earlier. The relative risk (RR)  
354 for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 –  
355 8.5) for the higher dose and 2.5 (95% CI 1.0 – 6.4) for the lower dose of CELEBREX  
356 compared to placebo. The absolute risk for the composite endpoint was 3.0% for the  
357 higher dose of CELEBREX, 2.2% for the lower dose of CELEBREX, and 0.9% for placebo.

358

359 The second long-term study, PreSAP (Prevention of Colorectal Sporadic Adenomatous  
360 Polyps) compared CELEBREX 400 mg once daily to placebo. Preliminary safety  
361 information from this trial demonstrated no increased cardiovascular risk for the  
362 composite endpoint of cardiovascular death, MI or stroke. The reason for the differing  
363 results for CV events in the APC and PreSAP trials is not known.

364

365 Clinical trials of other COX-2 selective and nonselective NSAIDs of up to three-years  
366 duration have shown an increased risk of serious cardiovascular thrombotic events,  
367 myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are  
368 considered potentially associated with this risk.

369

### 370 *Endoscopic Studies*

371 The correlation between findings of short-term endoscopic studies with CELEBREX and  
372 the relative incidence of clinically significant serious upper GI events with long-term use  
373 has not been established.

374

375 A randomized, double-blind study in 430 RA patients was conducted in which an  
376 endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers  
377 in patients taking CELEBREX 200 mg twice daily was 4% vs. 15% for patients taking  
378 diclofenac SR 75 mg twice daily. However, CELEBREX was not statistically different  
379 than diclofenac for clinically relevant GI outcomes in the CLASS trial (see **Special**

380 **Studies - CLASS).**

381

382 The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled  
383 studies in 2157 OA and RA patients in whom baseline endoscopies revealed no ulcers.

384 There was no dose relationship for the incidence of gastroduodenal ulcers and the dose of  
385 CELEBREX (50 mg to 400 mg twice daily). The incidence for naproxen 500 mg twice  
386 daily was 16.2 and 17.6% in the two studies, for placebo was 2.0 and 2.3%, and for all  
387 doses of CELEBREX the incidence ranged between 2.7%-5.9%. There have been no large,  
388 clinical outcome studies to compare clinically relevant GI outcomes with CELEBREX and  
389 naproxen.

390

391 In the endoscopic studies, approximately 11% of patients were taking aspirin ( $\leq$  325  
392 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in  
393 aspirin users than in non-users. However, the increased rate of ulcers in these aspirin  
394 users was less than the endoscopic ulcer rates observed in the active comparator groups,  
395 with or without aspirin.

396

397 Serious clinically significant upper GI bleeding has been observed in patients receiving  
398 CELEBREX in controlled and open-labeled trials (see **Special Studies - CLASS** and  
399 **WARNINGS – Gastrointestinal (GI) Effects-Risk of GI Ulceration, Bleeding, and**  
400 **Perforation**).

401

402

403

404

## INDICATIONS AND USAGE

405

406 Carefully consider the potential benefits and risks of CELEBREX and other treatment  
407 options before deciding to use CELEBREX. Use the lowest effective dose for the shortest  
408 duration consistent with individual patient treatment goals (see **WARNINGS**).

409

410 CELEBREX is indicated:

411 1) For relief of the signs and symptoms of osteoarthritis.

412

413 2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

414

415 3) For relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2  
416 years and older (see **CLINICAL STUDIES** and **ADVERSE REACTIONS - Adverse**  
417 **Events from JRA Study**).

418

419 4) For the relief of signs and symptoms of ankylosing spondylitis.

420

421 5) For the management of acute pain in adults (see **CLINICAL STUDIES**).

422

423 6) For the treatment of primary dysmenorrhea.

424

425 7) To reduce the number of adenomatous colorectal polyps in familial adenomatous  
426 polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is  
427 not known whether there is a clinical benefit from a reduction in the number of colorectal  
428 polyps in FAP patients. It is also not known whether the effects of CELEBREX treatment  
429 will persist after CELEBREX is discontinued. The efficacy and safety of CELEBREX  
430 treatment in patients with FAP beyond six months have not been studied (see  
431 **CLINICAL STUDIES, WARNINGS** and **PRECAUTIONS** sections).

## 432 433 434 **CONTRAINDICATIONS**

435  
436 CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

437  
438 CELEBREX should not be given to patients who have demonstrated allergic-type  
439 reactions to sulfonamides.

440  
441 CELEBREX should not be given to patients who have experienced asthma,  
442 urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely  
443 fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see  
444 **WARNINGS — Anaphylactoid Reactions**, and **PRECAUTIONS — Preexisting**  
445 **Asthma**).

446  
447 CELEBREX is contraindicated for the treatment of peri-operative pain in the setting  
448 of coronary artery bypass graft (CABG) surgery (see **WARNINGS**)

## 449 450 451 **WARNINGS**

### 452 453 **Cardiovascular Effects**

#### 454 ***Cardiovascular Thrombotic Events***

455 Chronic use of CELEBREX may cause an increased risk of serious adverse cardiovascular  
456 thrombotic events, myocardial infarction, and stroke, which can be fatal. In the APC  
457 trial, the relative risk for the composite endpoint of cardiovascular death, MI, or stroke  
458 was 3.4 (95% CI 1.4 – 8.5) for CELEBREX 400 mg twice daily and 2.5 (95% CI 1.0 – 6.4)  
459 for the CELEBREX 200 mg twice daily compared to placebo (see **Special Studies –**  
460 ***Adenomatous Polyp Studies***).

461  
462 All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients  
463 with known CV disease or risk factors for CV disease may be at greater risk. To  
464 minimize the potential risk for an adverse CV event in patients treated with CELEBREX,  
465 the lowest effective dose should be used for the shortest duration possible. Physicians  
466 and patients should remain alert for the development of such events, even in the absence  
467 of previous CV symptoms. Patients should be informed about the signs and/or symptoms  
468 of serious CV toxicity and the steps to take if they occur.

469  
470 There is no consistent evidence that concurrent use of aspirin mitigates the increased risk

471 of serious CV thrombotic events associated with NSAID use. The concurrent use of  
472 aspirin and CELEBREX does increase the risk of serious GI events (see **GI WARNINGS-**  
473 **Risk of GI Ulceration, Bleeding, and Perforation**).

474  
475 Two large, controlled, clinical trials of a different COX-2 selective NSAID for the  
476 treatment of pain in the first 10-14 days following CABG surgery found an increased  
477 incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

#### 478 479 ***Hypertension***

480 As with all NSAIDS, CELEBREX can lead to the onset of new hypertension or worsening  
481 of pre-existing hypertension, either of which may contribute to the increased incidence of  
482 CV events. Patients taking thiazides or loop diuretics may have impaired response to  
483 these therapies when taking NSAIDs. NSAIDs, including CELEBREX, should be used  
484 with caution in patients with hypertension. Blood pressure should be monitored closely  
485 during the initiation of therapy with CELEBREX and throughout the course of therapy.  
486 The rates of hypertension from the CLASS trial in the CELEBREX, ibuprofen and  
487 diclofenac treated patients were 2.4%, 4.2% and 2.5%, respectively (see **Special Studies**  
488 **- CLASS**).

#### 489 490 ***Congestive Heart Failure and Edema***

491 Fluid retention and edema have been observed in some patients taking NSAIDs,  
492 including CELEBREX (see **ADVERSE REACTIONS**). In the CLASS study (see **Special**  
493 **Studies – CLASS**), the Kaplan-Meier cumulative rates at 9 months of peripheral edema  
494 in patients on CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA  
495 and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg three  
496 times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively.  
497 CELEBREX should be used with caution in patients with fluid retention or heart failure.

#### 498 499 **Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation**

500 NSAIDs, including CELEBREX, can cause serious gastrointestinal events including  
501 bleeding, ulceration, and perforation of the stomach, small intestine or large intestine,  
502 which can be fatal. These serious adverse events can occur at any time, with or without  
503 warning symptoms, in patients treated with NSAIDs. Only one in five patients who  
504 develop a serious upper GI adverse event on NSAID therapy is symptomatic.  
505 Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in  
506 the CLASS trial, and 2.19% for the subgroup on low dose ASA. Patients 65 years of age  
507 and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA (see  
508 **Special Studies - CLASS**). With longer duration of use of NSAIDs, there is a trend for  
509 increasing the likelihood of developing a serious GI event at some time during the course  
510 of therapy. However, even short-term therapy is not without risk.

511  
512 NSAIDs should be prescribed with extreme caution in patients with a prior  
513 history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of  
514 peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than  
515 10-fold increased risk for developing a GI bleed compared to patients with neither of  
516 these risk factors. Other factors that increase the risk of GI bleeding in patients treated

517 with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer  
518 duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health  
519 status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients  
520 and therefore special care should be taken in treating this population.

521

522 To minimize the potential risk for an adverse GI event, the lowest effective dose  
523 should be used for the shortest possible duration. Physicians and patients should remain  
524 alert for signs and symptoms of GI ulceration and bleeding during CELEBREX therapy and  
525 promptly initiate additional evaluation and treatment if a serious GI adverse event is  
526 suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should  
527 be considered.

528

### 529 **Renal Effects**

530 Long-term administration of NSAIDs has resulted in renal papillary necrosis and other  
531 renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins  
532 have a compensatory role in the maintenance of renal perfusion. In these patients,  
533 administration of an NSAID may cause a dose-dependent reduction in prostaglandin  
534 formation and, secondarily, in renal blood flow, which may precipitate overt renal  
535 decompensation. Patients at greatest risk of this reaction are those with impaired renal  
536 function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and  
537 the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the  
538 pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to  
539 those observed with comparator NSAIDs.

540

### 541 **Advanced Renal Disease**

542 No information is available from controlled clinical studies regarding the use of  
543 CELEBREX in patients with advanced renal disease. Therefore, treatment with CELEBREX  
544 is not recommended in these patients with advanced renal disease. If CELEBREX therapy  
545 must be initiated, close monitoring of the patient's renal function is advisable.

546

### 547 **Anaphylactoid Reactions**

548 As with NSAIDs in general, anaphylactoid reactions have occurred in patients without  
549 known prior exposure to CELEBREX. In post-marketing experience, rare cases of  
550 anaphylactic reactions and angioedema have been reported in patients receiving  
551 CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This  
552 symptom complex typically occurs in asthmatic patients who experience rhinitis with or  
553 without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking  
554 aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS** —  
555 **Preexisting Asthma**). Emergency help should be sought in cases where an  
556 anaphylactoid reaction occurs.

557

558

559

### 560 **Skin Reactions**

561 CELEBREX is a sulfonamide and can cause serious skin adverse events such as exfoliative  
562 dermatitis, Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TENS),

563 which can be fatal. These serious events can occur without warning and in patients  
564 without prior known sulfa allergy. Patients should be informed about the signs and  
565 symptoms of serious skin manifestations and use of the drug should be discontinued at  
566 the first appearance of skin rash or any other sign of hypersensitivity.

567

### 568 **Pregnancy**

569 In late pregnancy CELEBREX should be avoided because it may cause premature closure  
570 of the ductus arteriosus (see **PRECAUTIONS – Pregnancy**).

571

572 **Familial Adenomatous Polyposis (FAP): Treatment with CELEBREX in FAP has not**  
573 **been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic**  
574 **colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients**  
575 **should not be altered because of the concurrent administration of CELEBREX. In**  
576 **particular, the frequency of routine endoscopic surveillance should not be decreased**  
577 **and prophylactic colectomy or other FAP-related surgeries should not be delayed.**

578

579

580

## 580 **PRECAUTIONS**

581

582 **General:** CELEBREX cannot be expected to substitute for corticosteroids or to treat  
583 corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to  
584 exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid  
585 therapy should have their therapy tapered slowly if a decision is made to discontinue  
586 corticosteroids.

587

588 The pharmacological activity of CELEBREX in reducing inflammation, and  
589 possibly fever, may diminish the utility of these diagnostic signs in detecting infectious  
590 complications of presumed noninfectious, painful conditions.

591

592 **Hepatic Effects:** Borderline elevations of one or more liver associated enzymes may  
593 occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST  
594 (approximately 3 or more times the upper limit of normal) have been reported in  
595 approximately 1% of patients in clinical trials with NSAIDs. These laboratory  
596 abnormalities may progress, may remain unchanged, or may be transient with continuing  
597 therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant  
598 hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported  
599 with NSAIDs, including CELEBREX (see **ADVERSE REACTIONS – post-marketing**  
600 **experience**). In controlled clinical trials of CELEBREX, the incidence of borderline  
601 elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of  
602 normal) of liver associated enzymes was 6% for CELEBREX and 5% for placebo, and  
603 approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo  
604 had notable elevations of ALT and AST.

605

606 A patient with symptoms and/or signs suggesting liver dysfunction, or in whom  
607 an abnormal liver test has occurred, should be monitored carefully for evidence of the  
608 development of a more severe hepatic reaction while on therapy with CELEBREX. If

609 clinical signs and symptoms consistent with liver disease develop, or if systemic  
610 manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

611

612 **Hematological Effects:** Anemia is sometimes seen in patients receiving CELEBREX. In  
613 controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4%  
614 with placebo. Patients on long-term treatment with CELEBREX should have their  
615 hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or  
616 blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT),  
617 or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at  
618 indicated dosages (see **CLINICAL PHARMACOLOGY—Platelets**).

619

### 620 **Systemic Onset Juvenile Rheumatoid Arthritis**

621 CELEBREX should be used only with caution in pediatric patients with systemic onset  
622 JRA due to the risk for serious adverse reactions including disseminated intravascular  
623 coagulation.

624

625 **Preexisting Asthma:** Patients with asthma may have aspirin-sensitive asthma. The use  
626 of aspirin in patients with aspirin-sensitive asthma has been associated with severe  
627 bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm,  
628 between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such  
629 aspirin-sensitive patients, CELEBREX should not be administered to patients with this  
630 form of aspirin sensitivity and should be used with caution in patients with preexisting  
631 asthma.

632

### 633 **Information for Patients**

634 Patients should be informed of the following information before initiating therapy with  
635 CELEBREX and periodically during the course of ongoing therapy. Patients should also be  
636 encouraged to read the NSAID Medication Guide that accompanies each prescription  
637 dispensed.

638

639 1. CELEBREX, like other NSAIDs, may cause serious CV side effects such as MI or  
640 stroke, which may result in hospitalization and even death. Although serious CV  
641 events can occur without warning symptoms, patients should be alert for the signs  
642 and symptoms of chest pain, shortness of breath, weakness, slurring of speech,  
643 and should ask for medical advice if they observe any of these signs or symptoms.  
644 Patients should be apprised of the importance of this follow-up (see **WARNINGS**  
645 **- Cardiovascular Effects**).

645

646 2. CELEBREX, like other NSAIDs, can cause gastrointestinal discomfort and, rarely,  
647 more serious side effects, such as ulcers and bleeding, which may result in  
648 hospitalization and even death. Although serious GI tract ulcerations and  
649 bleeding can occur without warning symptoms, patients should be alert for the  
650 signs and symptoms of ulcerations and bleeding, and should ask for medical  
651 advice when they observe any signs or symptoms that are indicative of these  
652 disorders, including epigastric pain, dyspepsia, melena, and hematemesis.  
653 Patients should be apprised of the importance of this follow-up (see **WARNINGS**

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— **Gastrointestinal (GI) Effects – Risk of Gastrointestinal Ulceration, Bleeding, and Perforation).**

3. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible. CELEBREX is a sulfonamide and can cause serious skin side effects such as exfoliative dermatitis, SJS, and TENS, which may result in hospitalizations and even death. These reactions can occur with all NSAIDs, even non-sulfonamides. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients with prior history of sulfa allergy should not take CELEBREX.
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). Patients should be instructed that they should stop therapy and seek immediate medical therapy if these signs and symptoms occur.
6. Patients should be informed of the signs and symptoms of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms (see **WARNINGS – Anaphylactoid Reactions**).
7. Patients should be informed that in late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.
8. Patients with familial adenomatous polyposis (FAP) should be informed that CELEBREX has not been shown to reduce colorectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving CELEBREX.

**Laboratory Tests:**

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, CELEBREX should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality



699 was also seen in patients who received comparator NSAIDs in these studies. The clinical  
700 significance of this abnormality has not been established.

701

## 702 **Drug Interactions**

703 **General:** Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in  
704 the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should  
705 be done with caution.

706

707 *In vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of  
708 cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with  
709 drugs that are metabolized by P450 2D6.

710

711 **ACE-inhibitors:** Reports suggest that NSAIDs may diminish the antihypertensive effect  
712 of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given  
713 consideration in patients taking CELEBREX concomitantly with ACE-inhibitors.

714

715 **Aspirin:** CELEBREX can be used with low-dose aspirin. However, concomitant  
716 administration of aspirin with CELEBREX increases the rate of GI ulceration or other  
717 complications, compared to use of CELEBREX alone (see **CLINICAL STUDIES —**  
718 **Special Studies — CLASS, WARNINGS – Gastrointestinal (GI) Effects – Risk of GI**  
719 **Ulceration, Bleeding, and Perforation, and WARNINGS – Cardiovascular Effects**).

720

721 **Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for**  
722 **cardiovascular prophylaxis.**

723

724 **Fluconazole:** Concomitant administration of fluconazole at 200 mg QD resulted in a  
725 two-fold increase in celecoxib plasma concentration. This increase is due to the  
726 inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see **Pharmacokinetics**  
727 **— Metabolism**). CELEBREX should be introduced at the lowest recommended dose in  
728 patients receiving fluconazole.

729

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

733

734 **Lithium:** In a study conducted in healthy subjects, mean steady-state lithium plasma  
735 levels increased approximately 17% in subjects receiving lithium 450 mg BID with  
736 CELEBREX 200 mg BID as compared to subjects receiving lithium alone. Patients on  
737 lithium treatment should be closely monitored when CELEBREX is introduced or  
738 withdrawn.

739

740 **Methotrexate:** In an interaction study of rheumatoid arthritis patients taking  
741 methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of  
742 methotrexate.

743

744 **Warfarin:** Anticoagulant activity should be monitored, particularly in the first few days,

745 after initiating or changing CELEBREX therapy in patients receiving warfarin or similar  
746 agents, since these patients are at an increased risk of bleeding complications. The effect  
747 of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy  
748 subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not  
749 alter the anticoagulant effect of warfarin as determined by prothrombin time. However,  
750 in post-marketing experience, serious bleeding events, some of which were fatal, have  
751 been reported, predominantly in the elderly, in association with increases in prothrombin  
752 time in patients receiving CELEBREX concurrently with warfarin.

753

### 754 **Animal Toxicology**

755 An increase in the incidence of background findings of spermatocele with or without  
756 secondary changes such as epididymal hypospermia as well as minimal to slight dilation  
757 of the seminiferous tubules was seen in the juvenile rat. These reproductive findings  
758 while apparently treatment-related did not increase in incidence or severity with dose and  
759 may indicate an exacerbation of a spontaneous condition. Similar reproductive findings  
760 were not observed in studies of juvenile or adult dogs or in adult rats treated with  
761 celecoxib. The clinical significance of this observation is unknown.

762

763 **Carcinogenesis, mutagenesis, impairment of fertility:** Celecoxib was not carcinogenic  
764 in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females  
765 (approximately 2- to 4-fold the human exposure as measured by the AUC<sub>0-24</sub> at 200 mg  
766 BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females  
767 (approximately equal to human exposure as measured by the AUC<sub>0-24</sub> at 200 mg BID) for  
768 two years.

769

770 Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese  
771 hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO  
772 cells and an *in vivo* micronucleus test in rat bone marrow.

773

774 Celecoxib did not impair male and female fertility in rats at oral doses up to 600  
775 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the  
776 AUC<sub>0-24</sub>).

777

### 778 **Pregnancy**

779 **Teratogenic effects:** Pregnancy Category C. Celecoxib at oral doses  $\geq 150$  mg/kg/day  
780 (approximately 2-fold human exposure at 200 mg BID as measured by AUC<sub>0-24</sub>), caused  
781 an increased incidence of ventricular septal defects, a rare event, and fetal alterations,  
782 such as ribs fused, sternbrae fused and sternbrae misshapen when rabbits were treated  
783 throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was  
784 observed when rats were given celecoxib at oral doses  $\geq 30$  mg/kg/day (approximately 6-  
785 fold human exposure based on the AUC<sub>0-24</sub> at 200 mg BID) throughout organogenesis.  
786 There are no studies in pregnant women. CELEBREX should be used during pregnancy  
787 only if the potential benefit justifies the potential risk to the fetus.

788

789 **Nonteratogenic effects:** Celecoxib produced pre-implantation and post-implantation  
790 losses and reduced embryo/fetal survival in rats at oral dosages  $\geq 50$  mg/kg/day

791 (approximately 6-fold human exposure based on the AUC<sub>0-24</sub> at 200 mg BID). These  
792 changes are expected with inhibition of prostaglandin synthesis and are not the result of  
793 permanent alteration of female reproductive function, nor are they expected at clinical  
794 exposures. No studies have been conducted to evaluate the effect of celecoxib on the  
795 closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the third  
796 trimester of pregnancy should be avoided.

797

798 **Labor and delivery:** Celecoxib produced no evidence of delayed labor or parturition at  
799 oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by  
800 the AUC<sub>0-24</sub> at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant  
801 women are unknown.

802

803 **Nursing mothers:** Celecoxib is excreted in the milk of lactating rats at concentrations  
804 similar to those in plasma. Limited data from one subject indicate that celecoxib is also  
805 excreted in human milk. Because many drugs are excreted in human milk and because of  
806 the potential for serious adverse reactions in nursing infants from CELEBREX, a decision  
807 should be made whether to discontinue nursing or to discontinue the drug, taking into  
808 account the importance of the drug to the mother.

809

#### 810 **Pediatric Use**

811 CELEBREX is approved for relief of the signs and symptoms of Juvenile Rheumatoid  
812 Arthritis in patients 2 years and older. Safety and efficacy have not been studied beyond  
813 six months in children. The long-term cardiovascular toxicity in children exposed to  
814 CELEBREX has not been evaluated and it is unknown if long-term risks may be similar to  
815 that seen in adults exposed to CELEBREX or other COX-2 selective and non-selective  
816 NSAIDs. (see **Boxed Warning, WARNINGS, and CLINICAL STUDIES**)

817

818 The use of celecoxib in patients 2 years to 17 years of age with pauciarticular,  
819 polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-  
820 week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a  
821 12-week open-label extension. Celecoxib has not been studied in patients under the age  
822 of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with  
823 active systemic features. Patients with systemic onset JRA (without active systemic  
824 features) appear to be at risk for the development of abnormal coagulation laboratory  
825 tests. In some patients with systemic onset JRA, both celecoxib and naproxen were  
826 associated with mild prolongation of activated partial thromboplastin time (APTT) but  
827 not prothrombin time (PT). NSAIDs including celecoxib should be used only with  
828 caution in patients with systemic onset JRA, due to the risk of disseminated intravascular  
829 coagulation. Patients with systemic onset JRA should be monitored for the development  
830 of abnormal coagulation tests. (see **CLINICAL PHARMACOLOGY – Pediatric,**  
831 **CLINICAL STUDIES – JRA, PRECAUTIONS – Systemic Onset JRA,**  
832 **PRECAUTIONS - Animal Toxicology, ADVERSE REACTIONS - Adverse events**  
833 **from JRA studies, and DOSAGE and ADMINISTRATION - JRA**).

834

#### 835 **Geriatric Use**

836 Of the total number of patients who received CELEBREX in clinical trials, more than  
837 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75  
838 years and over. No substantial differences in effectiveness were observed between these  
839 subjects and younger subjects. In clinical studies comparing renal function as measured  
840 by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and  
841 platelet aggregation, the results were not different between elderly and young volunteers.  
842 However, as with other NSAIDs, including those that selectively inhibit COX-2, there  
843 have been more spontaneous post-marketing reports of fatal GI events and acute renal  
844 failure in the elderly than in younger patients (see **WARNINGS – Gastrointestinal (GI)**  
845 **Effects – Risk of GI Ulceration, Bleeding, and Perforation**).

#### 846 847 **ADVERSE REACTIONS** 848

849 Of the CELEBREX treated patients in the premarketing controlled clinical trials,  
850 approximately 4,250 were patients with OA, approximately 2,100 were patients with RA,  
851 and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients  
852 have received a total daily dose of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or  
853 more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900  
854 patients have received CELEBREX at these doses for 6 months or more; approximately  
855 2,300 of these have received it for 1 year or more and 124 of these have received it for 2  
856 years or more.

857  
858 **Adverse events from CELEBREX premarketing controlled arthritis trials:** Table 3  
859 lists all adverse events, regardless of causality, occurring in  $\geq 2\%$  of patients receiving  
860 CELEBREX from 12 controlled studies conducted in patients with OA or RA that included  
861 a placebo and/or a positive control group. Since these 12 trials were of different  
862 durations, and patients in the trials may not have been exposed for the same duration of  
863 time, these percentages do not capture cumulative rates of occurrence.

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**Table 3**  
**Adverse Events Occurring in  $\geq 2\%$  of CELEBREX Patients**  
**From CELEBREX Premarketing Controlled Arthritis Trials**

	Celebrex (100-200 mg BID or 200 mg QD) (n=4146)	Placebo (n=1864)	Naproxen 500 mg BID (n=1366)	Diclofenac 75 mg BID (n=387)	Ibuprofen 800 mg TID (n=345)
<b>Gastrointestinal</b>					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
<b>Body as a whole</b>					
Back pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
<b>Central and peripheral nervous system</b>					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
<b>Psychiatric</b>					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
<b>Respiratory</b>					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
<b>Skin</b>					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.

**CELEBREX**

**(100 - 200 mg BID or 200 mg QD)**

**Gastrointestinal:** Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting

**Cardiovascular:** Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

**General:** Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

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930	<b>Resistance mechanism disorders:</b>	Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media
931		
932		
933	<b>Central, peripheral nervous system:</b>	Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo
934		
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936		
937	<b>Female reproductive:</b>	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis
938		
939		
940	<b>Male reproductive:</b>	Prostatic disorder
941		
942	<b>Hearing and vestibular:</b>	Deafness, ear abnormality, earache, tinnitus
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944		
945	<b>Heart rate and rhythm:</b>	Palpitation, tachycardia
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947	<b>Liver and biliary system:</b>	Hepatic function abnormal, SGOT increased, SGPT increased
948		
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951	<b>Metabolic and nutritional:</b>	BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase
952		
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955	<b>Musculoskeletal:</b>	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
956		
957		
958	<b>Platelets (bleeding or clotting):</b>	Ecchymosis, epistaxis, thrombocythemia
959		
960		
961	<b>Psychiatric:</b>	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
962		
963		
964	<b>Hemic:</b>	Anemia
965		
966		
967	<b>Respiratory:</b>	Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
968		
969		
970	<b>Skin and appendages:</b>	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
971		
972		
973	<b>Application site disorders:</b>	Cellulitis, dermatitis contact, injection site reaction, skin nodule
974		
975		
976	<b>Special senses:</b>	Taste perversion
977		
978	<b>Urinary system:</b>	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
979		
980		
981	<b>Vision:</b>	Blurred vision, cataract, conjunctivitis, eye pain, glaucoma
982		
983		
984	<b>Other serious adverse reactions which occur rarely (estimated &lt;0.1%), regardless of causality:</b> The following serious adverse events have occurred rarely in patients taking CELEBREX. Cases reported only in the post-marketing experience are indicated in italics.	
985		
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988	<b>Cardiovascular:</b>	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, <i>vasculitis, deep venous thrombosis</i>
989		

990		
991	<b>Gastrointestinal:</b>	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding,
992		esophageal perforation, pancreatitis, ileus
993		
994	<b>Liver and biliary system:</b>	Cholelithiasis, hepatitis, jaundice, liver failure
995		
996	<b>Hemic and</b>	
997	<b>lymphatic:</b>	Thrombocytopenia, agranulocytosis, aplastic anemia,
998		pancytopenia, leukopenia
999		
1000	<b>Metabolic:</b>	Hypoglycemia, hyponatremia
1001		
1002	<b>Nervous system:</b>	Ataxia, suicide, aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage (see
1003		PRECAUTIONS – Drug Interactions – Warfarin)
1004		
1005	<b>Renal:</b>	Acute renal failure, interstitial nephritis
1006		
1007	<b>Skin:</b>	Erythema multiforme, exfoliative dermatitis, Stevens-
1008		Johnson syndrome, toxic epidermal necrolysis
1009		
1010	<b>General:</b>	Sepsis, sudden death, anaphylactoid reaction, angioedema
1011		

## 1012 **Safety Data from CLASS Study:**

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### 1014 **Hematological Events:**

1015 During this study (see **Special Studies – CLASS**), the incidence of clinically significant  
 1016 decreases in hemoglobin (>2 g/dL) confirmed by repeat testing was lower in patients on  
 1017 CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses,  
 1018 respectively, and the approved dose for FAP) compared to patients on either diclofenac  
 1019 75 mg BID or ibuprofen 800 mg TID: 0.5%, 1.3% and 1.9%, respectively. The lower  
 1020 incidence of events with CELEBREX was maintained with or without ASA use (see  
 1021 **CLINICAL PHARMACOLOGY - Platelets**).

1022

### 1023 **Withdrawals/Serious Adverse Events:**

1024 Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for  
 1025 CELEBREX, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for  
 1026 serious adverse events (i.e. those causing hospitalization or felt to be life threatening or  
 1027 otherwise medically significant) regardless of causality were not different across  
 1028 treatment groups, respectively, 8%, 7%, and 8%.

1029

1030 **Adverse events from juvenile rheumatoid arthritis study:** In a 12-week, double-  
 1031 blind, active-controlled study, 242 JRA patients 2 years to 17 years of age were treated  
 1032 with celecoxib or naproxen; 77 JRA patients were treated with celecoxib 3 mg/kg BID,  
 1033 82 patients were treated with celecoxib 6 mg/kg BID, and 83 patients were treated with  
 1034 naproxen 7.5 mg/kg BID. The most commonly occurring ( $\geq 5\%$ ) adverse events in  
 1035 celecoxib treated patients were headache, fever (pyrexia), upper abdominal pain, cough,  
 1036 nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most  
 1037 commonly occurring ( $\geq 5\%$ ) adverse experiences for naproxen treated patients were  
 1038 headache, nausea, vomiting, fever, upper abdominal pain, diarrhea, cough, abdominal  
 1039 pain, and dizziness (Table 4). Compared with naproxen, celecoxib at doses of 3 and 6  
 1040 mg/kg BID had no observable deleterious effect on growth and development during the

1041 course of the 12-week double-blind study. There was no substantial difference in the  
 1042 number of clinical exacerbations of uveitis or systemic features of JRA among treatment  
 1043 groups.

1044

1045 In a 12-week, open-label extension of the double-blind study described above, 202 JRA  
 1046 patients were treated with celecoxib 6 mg/kg BID. The incidence of adverse events was  
 1047 similar to that observed during the double-blind study; no unexpected adverse events of  
 1048 clinical importance emerged.

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1050 **Table 4: Incidence of Adverse Events Occurring in ≥5% of JRA Patients in the**  
 1051 **Clinical Trial in Any Treatment Group by System Organ Class**

1052

System Organ Class/ Adverse Event Preferred Term	Celecoxib	Celecoxib	Naproxen
	3 mg/kg BID N=77	6 mg/kg BID N=82	7.5 mg/kg BID N=83
<b>Any Event, %</b>	<b>64</b>	<b>70</b>	<b>72</b>
<b>Eye Disorders</b>	<b>5</b>	<b>5</b>	<b>5</b>
<b>Gastrointestinal Disorders</b>	<b>26</b>	<b>24</b>	<b>36</b>
Abdominal pain NOS	4	7	7
Abdominal pain upper	8	6	10
Vomiting NOS	3	6	11
Diarrhea NOS	5	4	8
Nausea	7	4	11
<b>General Disorders and Administration Site Conditions</b>	<b>13</b>	<b>11</b>	<b>18</b>
Pyrexia	8	9	11
<b>Infections and Infestations</b>	<b>25</b>	<b>20</b>	<b>27</b>
Nasopharyngitis	5	6	5
<b>Injury and Poisoning</b>	<b>4</b>	<b>6</b>	<b>5</b>
<b>Investigations*</b>	<b>3</b>	<b>11</b>	<b>7</b>
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>	<b>8</b>	<b>10</b>	<b>17</b>
Arthralgia	3	7	4
<b>Nervous System Disorders</b>	<b>17</b>	<b>11</b>	<b>21</b>
Headache NOS	13	10	16
Dizziness (excluding vertigo)	1	1	7
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>8</b>	<b>15</b>	<b>15</b>
Cough	7	7	8
<b>Skin &amp; Subcutaneous Tissue Disorders</b>	<b>10</b>	<b>7</b>	<b>18</b>

1053 \*Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria  
 1054 NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased,  
 1055 Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present,  
 1056 Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS  
 1057 increased, Urine analysis abnormal NOS

1058

1059 **Adverse events from ankylosing spondylitis studies:** A total of 378 patients were  
 1060 treated with CELEBREX in placebo- and active- controlled ankylosing spondylitis studies.  
 1061 Doses up to 400 mg QD were studied. The types of adverse events reported in the  
 1062 ankylosing spondylitis studies were similar to those reported in the arthritis studies.



1063

1064 **Adverse events from analgesia and dysmenorrhea studies:** Approximately 1,700  
1065 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients  
1066 in post-oral surgery pain studies received a single dose of study medication. Doses up to  
1067 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic  
1068 surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea  
1069 studies were similar to those reported in arthritis studies. The only additional adverse  
1070 event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral  
1071 surgery pain studies.

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1073 **Adverse events from the controlled trial in familial adenomatous polyposis:** The  
1074 adverse event profile reported for the 83 patients with familial adenomatous polyposis  
1075 enrolled in the randomized, controlled clinical trial was similar to that reported for  
1076 patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only  
1077 new adverse event reported in the FAP trial, regardless of causality, and was observed in  
1078 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal  
1079 surgery.

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## OVERDOSAGE

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1084 No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 mg/day  
1085 for up to 10 days in 12 patients did not result in serious toxicity. Symptoms following  
1086 acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting,  
1087 and epigastric pain, which are generally reversible with supportive care. Gastrointestinal  
1088 bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma  
1089 may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic  
1090 ingestion of NSAIDs, and may occur following an overdose.

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1092 Patients should be managed by symptomatic and supportive care following an NSAID  
1093 overdose. There are no specific antidotes. No information is available regarding the  
1094 removal of celecoxib by hemodialysis, but based on its high degree of plasma protein  
1095 binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated  
1096 charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be  
1097 indicated in patients seen within 4 hours of ingestion with symptoms or following a large  
1098 overdose. Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may  
1099 not be useful due to high protein binding.

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## DOSAGE AND ADMINISTRATION

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1103 Carefully consider the potential benefits and risks of CELEBREX and other treatment  
1104 options before deciding to use CELEBREX. Use the lowest effective dose for the shortest  
1105 duration consistent with individual patient treatment goals (see **WARNINGS**).

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1107 For osteoarthritis and rheumatoid arthritis, the lowest dose of CELEBREX should be  
1108 sought for each patient. These doses can be given without regard to timing of meals.

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**Osteoarthritis:** For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice per day.

**Rheumatoid arthritis:** For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

**Juvenile Rheumatoid Arthritis:**

<b>Pediatric Patients (2 years and older)</b>	<b>Dose</b>
≥10 kg to ≤25 kg	50 mg capsule twice daily
>25 kg	100 mg capsule twice daily

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**Method of Administration**

For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2-8° C/ 35-45° F).

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**Ankylosing Spondylitis (AS):** For the management of the signs and symptoms of AS, the recommended dose of CELEBREX is 200 mg daily single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

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**Management of Acute Pain and Treatment of Primary Dysmenorrhea:** The recommended dose of CELEBREX is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

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**Familial adenomatous polyposis (FAP):** Usual medical care for FAP patients should be continued while on CELEBREX. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg twice per day to be taken with food.

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**Special Populations**

**Hepatic insufficiency:** The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by approximately 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended (see **CLINICAL PHARMACOLOGY – Special Populations**).

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**HOW SUPPLIED**

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CELEBREX 50-mg capsules are white, with reverse printed white on red band of body and cap with markings of 7767 on the cap and 50 on the body, supplied as:

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1153 **NDC Number**

**Size**

1154 0025-1515-01 bottle of 60

1155

1156 CELEBREX 100-mg capsules are white, reverse printed white on blue band of body and  
1157 cap with markings of 7767 on the cap and 100 on the body, supplied as:

1158 **NDC Number**

**Size**

1159 0025-1520-31 bottle of 100

1160 0025-1520-51 bottle of 500

1161 0025-1520-34 carton of 100 unit dose

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1163 CELEBREX 200-mg capsules are white, with reverse printed white on gold band with  
1164 markings of 7767 on the cap and 200 on the body, supplied as:

1165 **NDC Number**

**Size**

1166 0025-1525-31 bottle of 100

1167 0025-1525-51 bottle of 500

1168 0025-1525-34 carton of 100 unit dose

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1170 CELEBREX 400-mg capsules are white, with reverse printed white on green band with  
1171 markings of 7767 on the cap and 400 on the body, supplied as:

1172

1173 **NDC Number**

**Size**

1174 0025-1530-02 bottle of 60

1175 0025-1530-01 carton of 100 unit dose

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1177 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1178 Room Temperature].

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1180 Rx only Revised: December 2006

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*Distributed by*



**G.D. Searle LLC**

Division of Pfizer Inc, NY, NY 10017

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1186 **CELEBREX<sup>®</sup>**

1187 celecoxib capsules

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1189 LAB-0036-8.0

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**Medication Guide**  
**for**  
**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**  
(See the end of this Medication Guide for a list of prescription NSAID medicines.)

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

**NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.**

This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

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

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

- can happen without warning symptoms
- may cause death

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

- taking medicines called “corticosteroids” and “anticoagulants”
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

**NSAID medicines should only be used:**

- exactly as prescribed
  - at the lowest dose possible for your treatment
  - for the shortest time needed
- 

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

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

- different types of arthritis
- menstrual cramps and other types of short-term pain

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

**Do not take an NSAID medicine:**

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

**Tell your healthcare provider:**

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their**

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- **pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

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

<p><b>Serious side effects include:</b></p> <ul style="list-style-type: none"> <li>• heart attack</li> <li>• stroke</li> <li>• high blood pressure</li> <li>• heart failure from body swelling (fluid retention)</li> <li>• kidney problems including kidney failure</li> <li>• bleeding and ulcers in the stomach and intestine</li> <li>• low red blood cells (anemia)</li> <li>• life-threatening skin reactions</li> <li>• life-threatening allergic reactions</li> <li>• liver problems including liver failure</li> <li>• asthma attacks in people who have asthma</li> </ul>	<p><b>Other side effects include:</b></p> <ul style="list-style-type: none"> <li>• stomach pain</li> <li>• constipation</li> <li>• diarrhea</li> <li>• gas</li> <li>• heartburn</li> <li>• nausea</li> <li>• vomiting</li> <li>• dizziness</li> </ul>
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**Get emergency help right away if you have any of the following symptoms:**

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

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

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- skin rash or blisters with fever
- unusual weight gain
- swelling of the arms and legs, hands and feet

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

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

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

**NSAID medicines that need a prescription**

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid

<b>Generic Name</b>	<b>Tradename</b>
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-Naproxyn, Napreelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

\*

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