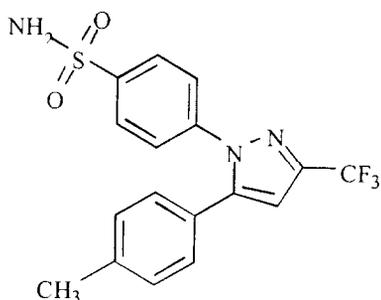


1 **CELEBREX™**  
2 (celecoxib capsules)

3  
4  
5 **DESCRIPTION**

6  
7 CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-  
8 (trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted  
9 pyrazole. It has the following chemical structure:  
10



11  
12  
13  
14 The empirical formula for celecoxib is  $C_{17}H_{14}F_3N_3O_2S$ , and the molecular weight is 381.38.

15  
16 CELEBREX oral capsules contain 100 mg and 200 mg of celecoxib.

17  
18 The inactive ingredients in CELEBREX capsules include: croscarmellose sodium, edible  
19 inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate  
20 and titanium dioxide.

21  
22 **CLINICAL PHARMACOLOGY**

23  
24 **Mechanism of Action**

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

31 **Pharmacokinetics**

32  
33 **Absorption**

34 Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Both peak  
35 plasma levels ( $C_{max}$ ) and area under the curve (AUC) are roughly dose proportional  
36 across the clinical dose range of 100-200 mg studied. At higher doses, under fasting  
37 conditions, there is a less than proportional increase in  $C_{max}$  and AUC which is thought  
38 to be due to the low solubility of the drug in aqueous media. Because of the low

39 solubility, absolute bioavailability studies have not been conducted. With multiple dosing,  
40 steady state conditions are reached on or before day 5.

41  
42 The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in  
43 Table 1.

44  
45 **Table 1: Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects<sup>1</sup>**

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

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

### 47 **Food Effects**

48 When CELEBREX capsules were taken with a high fat meal, peak plasma levels were  
49 delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%.  
50 Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid  
51 resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C<sub>max</sub>  
52 and 10% in AUC. CELEBREX capsules can be administered without regard to the timing  
53 of meals.  
54

### 55 **Distribution**

56 In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose  
57 range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser  
58 extent,  $\alpha_1$ -acid glycoprotein. The apparent volume of distribution at steady state (V<sub>ss</sub>/F) is  
59 approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not  
60 preferentially bound to red blood cells.  
61

### 62 **Metabolism**

63 Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites,  
64 a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have  
65 been identified in human plasma. These metabolites are inactive as COX-1 or COX-2  
66 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based  
67 on a previous history should be administered celecoxib with caution as they may have  
68 abnormally high plasma levels due to reduced metabolic clearance.  
69

### 70 **Excretion**

71 Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged  
72 drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug,  
73 approximately 57% of the dose was excreted in the feces and 27% was excreted into the  
74 urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite  
75 (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears  
76 that the low solubility of the drug prolongs the absorption process making terminal half-  
77 life (t<sub>1/2</sub>) determinations more variable. The effective half-life is approximately 11 hours  
78 under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.  
79  
80  
81

82 **Special Populations**

83

84 ***Geriatric***

85 At steady state, elderly subjects (over 65 years old) had a 40% higher C<sub>max</sub> and a 50%  
86 higher AUC compared to the young subjects. In elderly females, celecoxib C<sub>max</sub> and  
87 AUC are higher than those for elderly males, but these increases are predominantly due to  
88 lower body weight in elderly females. Dose adjustment in the elderly is not generally  
89 necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the  
90 lowest recommended dose.

91

92 ***Pediatric***

93 CELEBREX capsules have not been investigated in pediatric patients below 18 years of  
94 age.

95

96 ***Race***

97 Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher  
98 AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance  
99 of this finding is unknown.

100

101 ***Hepatic Insufficiency***

102 A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-  
103 Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased  
104 about 40% and 180%, respectively, above that seen in healthy control subjects.  
105 Therefore, CELEBREX capsules should be introduced at a reduced dose in patients with  
106 moderate hepatic impairment. Patients with severe hepatic impairment have not been  
107 studied. The use of CELEBREX in patients with severe hepatic impairment is not  
108 recommended.

109

110 ***Renal Insufficiency***

111 In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients  
112 with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with  
113 normal renal function. No significant relationship was found between GFR and celecoxib  
114 clearance. Patients with severe renal insufficiency have not been studied.

115

116 **~~Drug Interactions~~**

117

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

119

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

123

124 Clinical studies with celecoxib have identified potentially significant interactions with  
125 fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs)  
126 suggests the potential for interactions with furosemide and ACE inhibitors. The effects of

127 celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole,  
128 methotrexate, phenytoin, tolbutamide, and warfarin have been studied *in vivo* and  
129 clinically important interactions have not been found.

130

## 131 **CLINICAL STUDIES**

132

133 **Osteoarthritis (OA):** CELEBREX has demonstrated significant reduction in joint pain  
134 compared to placebo. CELEBREX was evaluated for treatment of the signs and the  
135 symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and  
136 active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment  
137 with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in WOMAC  
138 (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain,  
139 stiffness, and functional measures in OA. In three 12-week studies of pain accompanying  
140 OA flare, CELEBREX doses of 100mg BID and 200mg BID provided significant  
141 reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BID or  
142 200 mg BID the effectiveness of CELEBREX was shown to be similar to that of  
143 naproxen 500 mg BID. Doses of 200 mg BID provided no additional benefit above that  
144 seen with 100 mg BID. A total daily dose of 200 mg has been shown to be equally  
145 effective whether administered as 100 mg BID or 200 mg QD.

146

147 **Rheumatoid Arthritis (RA):** CELEBREX has demonstrated significant reduction in  
148 joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated  
149 for treatment of the signs and symptoms of RA in approximately 2,100 patients in  
150 placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX  
151 was shown to be superior to placebo in these studies, using the ACR20 Responder Index,  
152 a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of  
153 100 mg BID and 200 mg BID were similar in effectiveness and both were comparable to  
154 naproxen 500 mg BID.

155

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

159

## 160 **Special Studies**

161 **Gastrointestinal:** Scheduled upper GI endoscopic evaluations were performed in over  
162 4,500 arthritis patients who were enrolled in five controlled randomized 12-24 week trials  
163 using active comparators, two of which also included placebo controls. Twelve-week  
164 endoscopic ulcer data are available on approximately 1,400 patients and 24 week  
165 endoscopic ulcer data are available on 184 patients on CELEBREX at doses ranging from  
166 50-400 mg BID. In all three studies that included naproxen 500 mg BID, and in the study  
167 that included ibuprofen 800 mg TID, CELEBREX was associated with a statistically  
168 significantly lower incidence of endoscopic ulcers over the study period. Two studies  
169 compared CELEBREX with diclofenac 75 mg BID; one study revealed a statistically  
170 significantly higher prevalence of endoscopic ulcers in the diclofenac group at the study  
171 endpoint (6 months on treatment), and one study revealed no statistically significant

172 difference between cumulative endoscopic ulcer incidence rates in the diclofenac and  
 173 CELEBREX groups after 1, 2, and 3 months of treatment. There was no consistent  
 174 relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX  
 175 over the range studied.

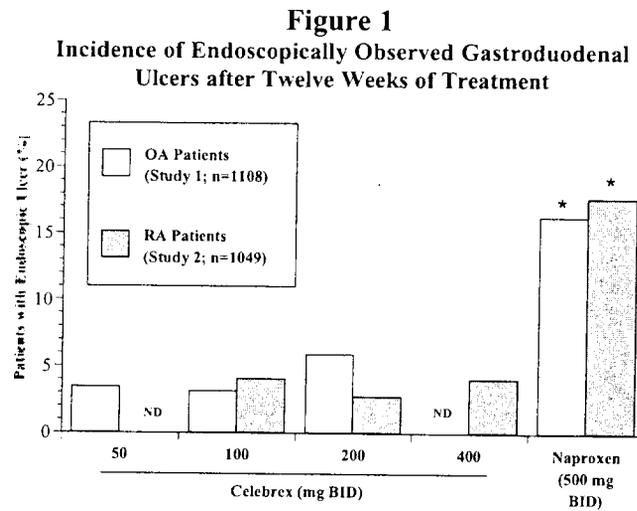
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177 Figure 1 and Table 2 summarize the incidence of endoscopic ulcers in two 12-week  
 178 studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

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ND = Not Done

\* Significantly different from all other treatments;  $p < 0.05$ .

Celebrex 100 mg BID and 200 mg QD, BID are the recommended doses.

These studies were not powered to compare the endoscopic ulcer rates of Celebrex vs. placebo.

Study 1: placebo ulcer rate = 2.3%

Study 2: placebo ulcer rate = 2.0%

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**Table 2**  
**Incidence of Gastroduodenal Ulcers from Endoscopic Studies  
 in OA and RA Patients**

	3 Month Studies	
	Study 1 (n = 1108)	Study 2 (n = 1049)
Placebo	2.3% (5/217)	2.0% (4/200)
Celebrex 50 mg BID	3.4% (8/233)	---
Celebrex 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celebrex 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celebrex 400 mg BID	---	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

\*  $p \leq 0.05$  vs all other treatments

207 Figure 2 and Table 3 summarize data from two 12-week studies that enrolled patients in  
 208 whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies  
 209 every 4 weeks to give information on ulcer risk over time.

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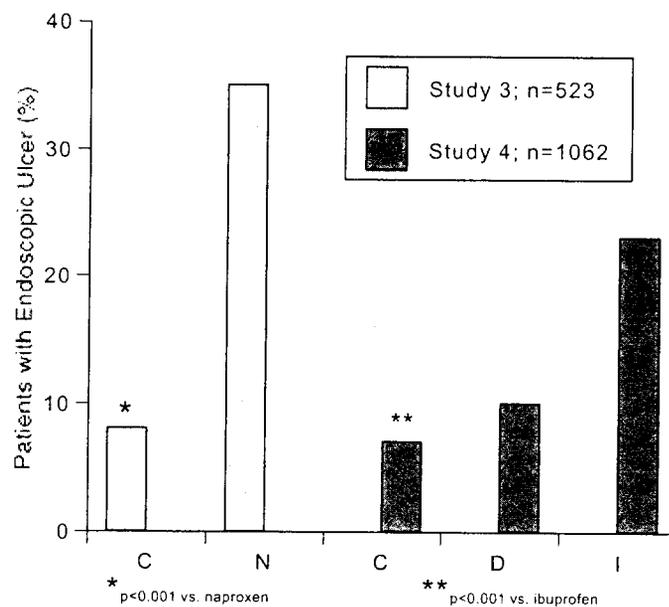
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**Figure 2**  
**Cumulative Incidence of Gastroduodenal Ulcers Based on 4 Serial Endoscopies Over 12 Weeks**



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**Table 3**  
**Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients**

	Week 4	Week 8	Week 12	Final
<b>Study 3 (n=523)</b>				
Celebrex 200 mg BID	4.0% (10/252)*	2.2% (5/227)	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BID	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (89/257)
<b>Study 4 (n=1062)</b>				
Celebrex 200 mg BID	3.9% (13/337)†	2.4% (7/296)†	1.8% (5/274)†	7.0% (25/356)†
Diclofenac 75 mg BID	5.1% (18/350)	3.3% (10/306)	2.9% (8/278)	9.7% (36/372)
Ibuprofen 800 mg TID	13.0% (42/323)	6.2% (15/241)	9.6% (21/219)	23.3% (78/334)

\*p ≤ 0.05 Celebrex vs. naproxen based on interval and cumulative analyses

† p ≤ 0.05 Celebrex vs. ibuprofen based on interval and cumulative analyses

240

241

One randomized and double-blinded 6-month study in 430 RA patients was conducted in which

242 an endoscopic examination was performed at 6 months. The results are shown in  
243 Figure 3.

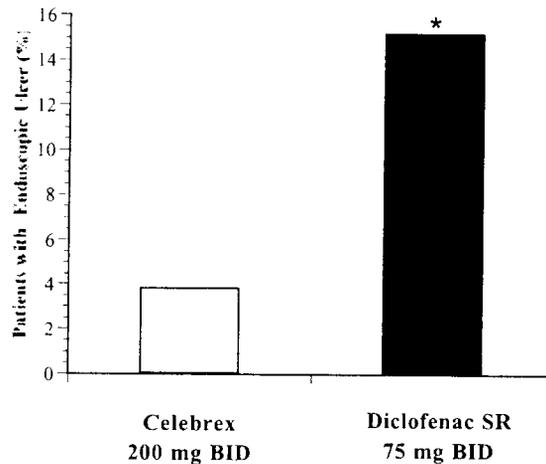
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**Figure 3**

**Prevalence of Endoscopically Observed Gastroduodenal Ulcers after Six Months of Treatment in Patients with Rheumatoid Arthritis**



\* Significantly different from Celebrex;  $p < 0.001$

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

**Use with Aspirin:** Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin ( $\leq 325$  mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

**Platelets:** In clinical trials, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg BID for up to 7 days duration (higher than recommended therapeutic doses) had no effect on platelet aggregation and bleeding time. Comparators (naproxen 500 mg BID, ibuprofen 800 mg TID, diclofenac 75 mg BID) significantly reduced platelet aggregation and prolonged bleeding time.

## INDICATIONS AND USAGE

271 CELEBREX is indicated:

272

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

274

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

276

## 277 **CONTRAINDICATIONS**

278

279 CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

280

281 CELEBREX should not be given to patients who have demonstrated allergic-type  
282 reactions to sulfonamides.

283

284 CELEBREX should not be given to patients who have experienced asthma, urticaria, or  
285 allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal,  
286 anaphylactic-like reactions to NSAIDs have been reported in such patients (see  
287 WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

288

## 289 **WARNINGS**

290

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

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

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

307

308 It is unclear, at the present time, how the above rates apply to CELEBREX (see  
309 CLINICAL STUDIES-Special Studies). Among 5,285 patients who received  
310 CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month  
311 studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI  
312 bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285  
313 patients were in studies that required them to be free of ulcers by endoscopy at study  
314 entry. Thus it is unclear if this study population is representative of the general population.  
315 Prospective, long-term studies required to compare the incidence of serious, clinically

316 significant upper GI adverse events in patients taking CELEBREX vs comparator NSAID  
317 products have not been performed.

318

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

325

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

333

#### 334 **Anaphylactoid Reactions**

335 Anaphylactoid reactions were not reported in patients receiving CELEBREX in clinical  
336 trials. However, as with NSAIDs in general, anaphylactoid reactions may occur in  
337 patients without known prior exposure to CELEBREX. CELEBREX should not be given  
338 to patients with the aspirin triad. This symptom complex typically occurs in asthmatic  
339 patients who experience rhinitis with or without nasal polyps, or who exhibit severe,  
340 potentially fatal bronchospasm after taking aspirin or other NSAIDs (see  
341 CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help  
342 should be sought in cases where an anaphylactoid reaction occurs.

343

#### 344 **Advanced Renal Disease**

345 No information is available regarding the use of CELEBREX in patients with advanced  
346 kidney disease. Therefore, treatment with CELEBREX is not recommended in these  
347 patients. If CELEBREX therapy must be initiated, close monitoring of the patient's  
348 kidney function is advisable (see PRECAUTIONS - Renal Effects).

349

#### 350 **Pregnancy—**

351 In late pregnancy CELEBREX should be avoided because it may cause premature closure  
352 of the ductus arteriosus.

353

### 354 **PRECAUTIONS**

#### 355 **General**

356 CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid  
357 insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of  
358 corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should  
359 have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

360

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

364

365 ***Hepatic Effects:***

366 Borderline elevations of one or more liver tests may occur in up to 15% of patients taking  
367 NSAIDs, and notable elevations of ALT or AST (approximately three or more times the  
368 upper limit of normal) have been reported in approximately 1% of patients in clinical trials  
369 with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or  
370 may be transient with continuing therapy. Rare cases of severe hepatic reactions,  
371 including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some  
372 with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of  
373 CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX  
374 and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of  
375 patients taking placebo had notable elevations of ALT and AST.

376

377 A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an  
378 abnormal liver test has occurred, should be monitored carefully for evidence of the  
379 development of a more severe hepatic reaction while on therapy with CELEBREX. If  
380 clinical signs and symptoms consistent with liver disease develop, or if systemic  
381 manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

382

383 ***Renal Effects:***

384 Long-term administration of NSAIDs has resulted in renal papillary necrosis and other  
385 renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins  
386 have a compensatory role in the maintenance of renal perfusion. In these patients,  
387 administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent  
388 reduction in prostaglandin formation and, secondarily, in renal blood flow, which may  
389 precipitate overt renal decompensation. Patients at greatest risk of this reaction are those  
390 with impaired renal function, heart failure, liver dysfunction, those taking diuretics and  
391 ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by  
392 recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal  
393 effects similar to those observed with comparator NSAIDs.

394

395 Caution should be used when initiating treatment with CELEBREX in patients with  
396 considerable dehydration. It is advisable to rehydrate patients first and then start therapy  
397 with CELEBREX. Caution is also recommended in patients with pre-existing kidney  
398 disease (see WARNINGS-Advanced Renal Disease).

399

400 ***Hematological Effects:***

401 Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials  
402 the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on  
403 long-term treatment with CELEBREX should have their hemoglobin or hematocrit  
404 checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does  
405 not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time

406 (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (See  
407 CLINICAL STUDIES-Special Studies-Platelets).

408

409 ***Fluid Retention and Edema:***

410 Fluid retention and edema have been observed in some patients taking CELEBREX (see  
411 ADVERSE REACTIONS). Therefore, CELEBREX should be used with caution in  
412 patients with fluid retention, hypertension, or heart failure.

413

414 ***Preexisting Asthma:***

415 Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with  
416 aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal.  
417 Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal  
418 anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX  
419 should not be administered to patients with this form of aspirin sensitivity and should be  
420 used with caution in patients with preexisting asthma.

421

422 **Information for Patients**

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

430

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

433

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

438

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

441

442 In late pregnancy CELEBREX should be avoided because it may cause premature closure  
443 of the ductus arteriosus.

444

445 **Laboratory Tests**

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

448

449 During the controlled clinical trials, there was an increased incidence of hyperchloremia in  
450 patients receiving celecoxib compared with patients on placebo. Other laboratory

451 abnormalities that occurred more frequently in the patients receiving celecoxib included  
452 hypophosphatemia, and elevated BUN. These laboratory abnormalities were also seen in  
453 patients who received comparator NSAIDs in these studies. The clinical significance of  
454 these abnormalities has not been established.

455

#### 456 **Drug Interactions**

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

460

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

464

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

468

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

472

473 **Aspirin:** CELEBREX can be used with low dose aspirin. However, concomitant  
474 administration of aspirin with CELEBREX may result in an increased rate of GI ulceration  
475 or other complications, compared to use of CELEBREX alone (see CLINICAL  
476 STUDIES- Special Studies - Gastrointestinal). Because of its lack of platelet effects,  
477 CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

478

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

484

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

490

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

494

495 **Warfarin:** The effect of celecoxib on the anti-coagulant effect of warfarin was studied in  
496 a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects,  
497 celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin  
498 time. However, caution should be used when administering CELEBREX with warfarin  
499 since these patients are at increased risk of bleeding complications.

500

501 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Celecoxib was not  
502 carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females  
503 (approximately 2-4 fold the human exposure as measured by the AUC<sub>0-24</sub> at 200 mg BID)  
504 or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females  
505 (approximately equal to human exposure as measured by the AUC<sub>0-24</sub> at 200 mg BID) for  
506 two years.

507

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

511

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

515

516 **Pregnancy:**

517 **Teratogenic effects:** Pregnancy Category C. Celecoxib was not teratogenic in rabbits up  
518 to an oral dose of 60 mg/kg/day (equal to human exposure at 200 mg BID as measured by  
519 AUC<sub>0-24</sub>); however, at oral doses  $\geq$  150 mg/kg/day (approximately 2-fold human exposure  
520 at 200 mg BID as measured by AUC<sub>0-24</sub>), an increased incidence of fetal alterations, such  
521 as ribs fused, sternebrae fused and sternebrae misshapen, was observed. A dose-  
522 dependent increase in diaphragmatic hernias was observed in one of two rat studies at oral  
523 doses  $\geq$  30 mg/kg/day (approximately 6-fold human exposure based on the AUC<sub>0-24</sub> at 200  
524 mg BID). There are no studies in pregnant women. CELEBREX should be used during  
525 pregnancy only if the potential benefit justifies the potential risk to the fetus.

526

527 **Nonteratogenic effects:** Celecoxib produced pre-implantation and post-implantation  
528 losses and reduced embryo/fetal survival in rats at oral dosages  $\geq$  50 mg/kg/day  
529 (approximately 6-fold human exposure based on the AUC<sub>0-24</sub> at 200 mg BID). These  
530 changes are expected with inhibition of prostaglandin synthesis and are not the result of  
531 permanent alteration of female reproductive function, nor are they expected at clinical  
532 exposures. No studies have been conducted to evaluate the effect of celecoxib on the  
533 closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the  
534 third trimester of pregnancy should be avoided.

535

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

540

541 **Nursing mothers** Celecoxib is excreted in the milk of lactating rats at concentrations  
 542 similar to those in plasma. It is not known whether this drug is excreted in human milk.  
 543 Because many drugs are excreted in human milk and because of the potential for serious  
 544 adverse reactions in nursing infants from CELEBREX, a decision should be made whether  
 545 to discontinue nursing or to discontinue the drug, taking into account the importance of  
 546 the drug to the mother.

547

548 **Pediatric Use**

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

551

552 **Geriatric Use**

553 Of the total number of patients who received CELEBREX in clinical trials, more than  
 554 2,100 were 65-74 years of age, while approximately 800 additional patients were 75 years  
 555 and over. While the incidence of adverse experiences tended to be higher in elderly  
 556 patients, no substantial differences in safety and effectiveness were observed between  
 557 these subjects and younger subjects. Other reported clinical experience has not identified  
 558 differences in response between the elderly and younger patients, but greater sensitivity of  
 559 some older individuals cannot be ruled out.

560

561 In clinical studies comparing renal function as measured by the GFR, BUN and creatinine,  
 562 and platelet function as measured by bleeding time and platelet aggregation, the results  
 563 were not different between elderly and young volunteers.

564

565 **ADVERSE REACTIONS**

566

567 Of the CELEBREX treated patients in controlled trials, approximately 4,250 were patients  
 568 with OA, approximately 2,100 were patients with RA, and approximately 1,050 were  
 569 patients with post-surgical pain. More than 8,500 patients have received a total daily dose  
 570 of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or more, including more than  
 571 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients have received  
 572 CELEBREX at these doses for 6 months or more; approximately 2,300 of these have  
 573 received it for 1 year or more and 124 of these have received it for 2 years or more.

574

575 **Adverse events from controlled trials:** Table 5 lists all adverse events, regardless of  
 576 causality, occurring in  $\geq 2\%$  of patients receiving CELEBREX from 12 controlled studies  
 577 conducted in patients with OA or RA that included a placebo and/or a positive control  
 578 group.

579

580

581

Table 4

Adverse Events Occurring in  $\geq 2\%$  Of Celebrex Patients

582

583

584

585

586

Celebrex (100-200 mg BID) and (200 mg QD)	Placebo	Naproxen 500 mg BID	Ibuprofen 800 mg TID	Diclofenac 75 mg BID
---	---------	------------------------	-------------------------	-------------------------

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	(N=4146)	(N=1864)	(N=1366)	(N=387)	(N=345)
587					
588					
589	<b>Gastrointestinal</b>				
590	Abdominal pain	4.1%	2.8%	7.7%	9.0%
591	Diarrhea	5.6%	3.8%	5.3%	9.3%
592	Dyspepsia	8.8%	6.2%	12.2%	10.9%
593	Flatulence	2.2%	1.0%	3.6%	4.1%
594	Nausea	3.5%	4.2%	6.0%	3.4%
595					
596	<b>Body as a whole</b>				
597					
598	Back Pain	2.8%	3.6%	2.2%	2.6%
599	Peripheral edema	2.1%	1.1%	2.1%	1.0%
600	Injury-accidental	2.9%	2.3%	3.0%	2.6%
601					
602	<b>Central and peripheral nervous system</b>				
603	Dizziness	2.0%	1.7%	2.6%	1.3%
604	Headache	15.8%	20.2%	14.5%	15.5%
605					
606	<b>Psychiatric</b>				
607	Insomnia	2.3%	2.3%	2.9%	1.3%
608					
609	<b>Respiratory</b>				
610	Pharyngitis	2.3%	1.1%	1.7%	1.6%
611	Rhinitis	2.0%	1.3%	2.4%	2.3%
612	Sinusitis	5.0%	4.3%	4.0%	5.4%
613	Upper resp. tract				
614	infection	8.1%	6.7%	9.9%	9.8%
615	<b>Skin</b>				
616	Rash	2.2%	2.1%	2.1%	1.3%
617					
618					

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)**

632	<b>Gastrointestinal</b>	Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, stomatitis, tooth disorder, vomiting
633		
634	<b>Cardiovascular</b>	Aggravated hypertension, dry mouth, glaucoma, tenesmus
635		
636	<b>General</b>	Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain
637		
638		
639		
640		
641	<b>Resistance Mechanism</b>	Herpes simplex, herpes zoster, infection bacterial, infection
642	<b>Disorders</b>	fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media
643		
644	<b>Central, peripheral</b>	Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy,
645	<b>nervous system</b>	paresthesia, vertigo
646		
647		
648	<b>Female reproductive</b>	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage,

649		vaginitis
650		
651	<b>Male reproductive</b>	Prostatic disorder
652		
653	<b>Hearing and vestibular</b>	Deafness, ear abnormality, earache, tinnitus
654		
655		
656	<b>Heart rate and rhythm</b>	Angina pectoris, coronary artery disorder, myocardial infarction, palpitation, tachycardia
657		
658		
659	<b>Liver and biliary system</b>	Hepatic function abnormal, SGOT increased, SGPT increased
660		
661		
662		
663	<b>Metabolic and nutritional</b>	BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase
664		
665		
666		
667		
668	<b>Musculoskeletal</b>	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
669		
670		
671	<b>Platelets (bleeding or clotting)</b>	Ecchymosis, epistaxis, thrombocythemia
672		
673		
674	<b>Psychiatric</b>	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
675		
676		
677	<b>Hemic</b>	Anemia
678		
679		
680	<b>Respiratory</b>	Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
681		
682		
683	<b>Skin and appendages</b>	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
684		
685		
686	<b>Application site disorders</b>	Cellulitis, dermatitis contact, injection site reaction, skin nodule
687		
688		
689	<b>Special senses</b>	Taste perversion
690		
691	<b>Urinary system</b>	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
692		
693		
694	<b>Vision</b>	Blurred vision, cataract, conjunctivitis, eye pain
695		
696	<b>Other serious adverse reactions which occur rarely (&lt;0.1%), regardless of causality:</b> The following serious adverse events have occurred rarely in patients, taking CELEBREX.	
697		
698		
699	<b>Cardiovascular:</b>	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis
700		
701		
702	<b>Gastrointestinal:</b>	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, cholelithiasis, ileus
703		
704		
705	<b>Hemic and lymphatic:</b>	Thrombocytopenia
706		
707		
708	<b>Nervous system:</b>	Ataxia

709

710 **Renal:** Acute renal failure

711

712 **General:** Sepsis, sudden death

713

714

715

## OVERDOSAGE

716

717 Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness,  
718 nausea, vomiting, and epigastric pain, which are generally reversible with supportive care.  
719 Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory  
720 depression and coma may occur, but are rare. Anaphylactoid reactions have been reported  
721 with therapeutic ingestion of NSAIDs, and may occur following an overdose.

722

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

731

732

## DOSAGE AND ADMINISTRATION

733

734 The lowest dose of CELEBREX should be sought for each patient.

735

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

738

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

741

742

## HOW SUPPLIED

743

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

746 **NDC Number**      **Size**

747 0025-1520-31 bottle of 100

748 0025-1520-34 carton of 100 unit dose

749

750

751

752

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

755

756 **NDC Number**      **Size**

757 0025-1525-31 bottle of 100

758 0025-1525-34 carton of 100 unit dose

759

760 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [ See USP**  
761 **Controlled Room Temperature]**

762

763 **Rx only**                      **Revised: (date)**

764

765

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771 *Marketed by:*772 *G.D. Searle & Co.*773 *Chicago IL 60680 USA*774 *Pfizer Inc.*775 *New York NY 10017 USA*

776

777 *Address medical inquiries to:*778 *G.D. Searle & Co.*779 *Healthcare Information Services*780 *5200 Old Orchard Rd.*781 *Skokie IL 60077*

782

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784

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787 (celecoxib capsules)

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790 (A05264)

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