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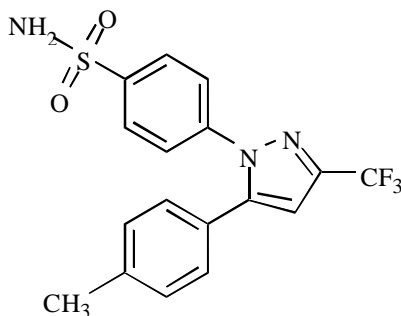
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1 **CELEBREX™**
2 (celecoxib capsules)

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5 **DESCRIPTION**

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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:



11
12
13
14 The empirical formula for celecoxib is C₁₇H₁₄F₃N₃O₂S, 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

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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 Subjects¹**

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

46

¹Subjects under fasting conditions (n=36, 19-52 yrs.)

47

48 ***Food Effects***

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

55

56 ***Distribution***

57 In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose
58 range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser
59 extent, α_1 -acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is
60 approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not
61 preferentially bound to red blood cells.

62

63 ***Metabolism***

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

70

71 ***Excretion***

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

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82 **Special Populations**

83

84 ***Geriatric***

85 At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50%
86 higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} 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

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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

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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.

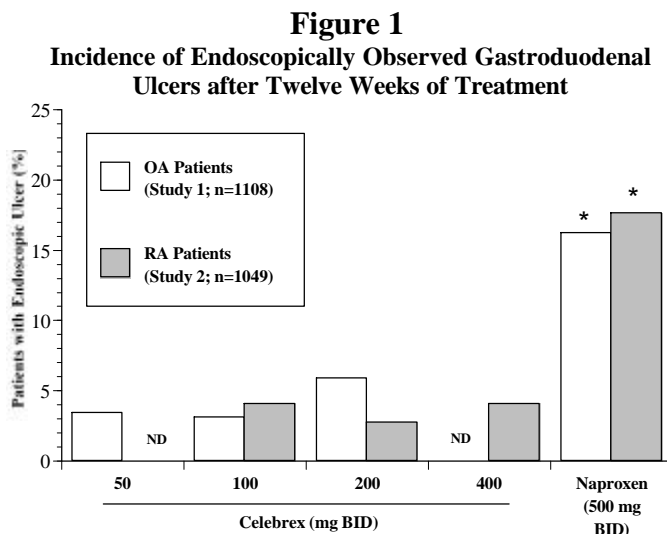
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177 Figure 1 and Table 2 summarize the incidence of endoscopic ulcers in two 12-week
 178 studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

179

180

181



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

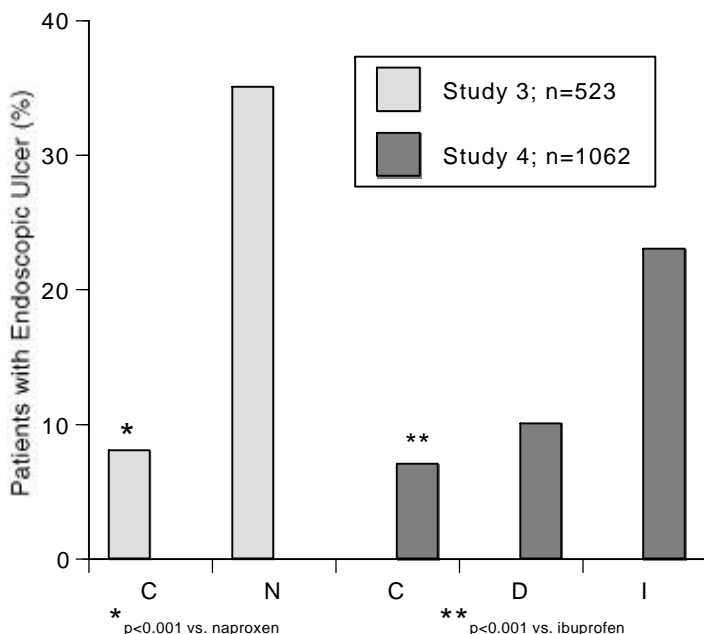
	3 Month Studies	
	Study 1 (n = 1108)	Study 2 (n= 1049)
Placebo	2.3% (5/217)	2.0% (4/200)
Celebrex 50 mg BID	3.4% (8/233)	---
Celebrex 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celebrex 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celebrex 400 mg BID	---	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

* $p \leq 0.05$ vs all other treatments

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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.

210
 211
 212 **Figure 2**
 213 **Cumulative Incidence of Gastroduodenal Ulcers Based on 4 Serial**
 214 **Endoscopies Over 12 Weeks**
 215



216
 217
 218 C = Celecoxib 200 mg BID D = Diclofenac 75 mg BID
 219 N = Naproxen 500 mg BID I = Ibuprofen 800 mg TID
 220

221
 222 **Table 3**
 223 **Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies**
 224 **in OA and RA Patients**
 225

	Week 4	Week 8	Week 12	Final
Study 3 (n=523)				
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)
Study 4 (n=1062)				
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)

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 237
 238 *p≤ 0.05 Celebrex vs. naproxen based on interval and cumulative analyses
 239 † 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

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

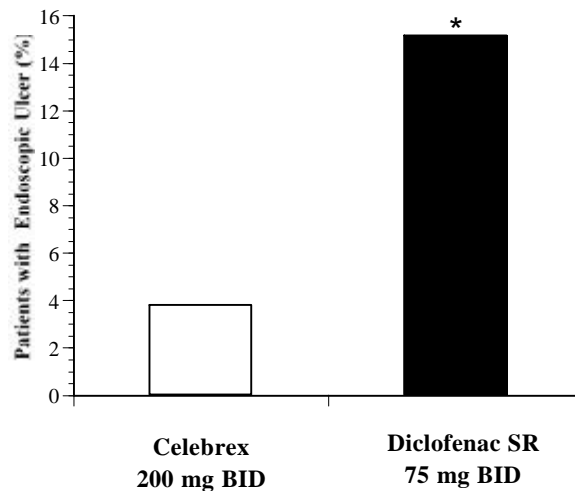
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Figure 3

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



* Significantly different from Celebrex; $p < 0.001$

247

248

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

256

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

262

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

268

269 **INDICATIONS AND USAGE**

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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

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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.

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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

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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

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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.

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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 AUC₀₋₂₄ 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 AUC₀₋₂₄ 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 AUC₀₋₂₄.

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 AUC₀₋₂₄); however, at oral doses \geq 150 mg/kg/day (approximately 2-fold human exposure
520 at 200 mg BID as measured by AUC₀₋₂₄), an increased incidence of fetal alterations, such
521 as ribs fused, sternbrae fused and sternbrae 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 AUC₀₋₂₄ 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 AUC₀₋₂₄ 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 AUC₀₋₂₄ at 200 mg BID). The effects of CELEBREX on labor and delivery in
539 pregnant women are unknown.

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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	Gastrointestinal				
590	Abdominal pain 4.1%	2.8%	7.7%	9.0%	9.0%
591	Diarrhea 5.6%	3.8%	5.3%	9.3%	5.8%
592	Dyspepsia 8.8%	6.2%	12.2%	10.9%	12.8%
593	Flatulence 2.2%	1.0%	3.6%	4.1%	3.5%
594	Nausea 3.5%	4.2%	6.0%	3.4%	6.7%
595					
596	Body as a whole				
597					
598	Back Pain 2.8%	3.6%	2.2%	2.6%	0.9%
599	Peripheral edema 2.1%	1.1%	2.1%	1.0%	3.5%
600	Injury-accidental 2.9%	2.3%	3.0%	2.6%	3.2%
601					
602	Central and peripheral nervous system				
603	Dizziness 2.0%	1.7%	2.6%	1.3%	2.3%
604	Headache 15.8%	20.2%	14.5%	15.5%	15.4%
605					
606	Psychiatric				
607	Insomnia 2.3%	2.3%	2.9%	1.3%	1.4%
608					
609	Respiratory				
610	Pharyngitis 2.3%	1.1%	1.7%	1.6%	2.6%
611	Rhinitis 2.0%	1.3%	2.4%	2.3%	0.6%
612	Sinusitis 5.0%	4.3%	4.0%	5.4%	5.8%
613	Upper resp. tract infection 8.1%	6.7%	9.9%	9.8%	9.9%
614					
615	Skin				
616	Rash 2.2%	2.1%	2.1%	1.3%	1.2%

617

618

619 In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events
620 was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among
621 the most common reasons for discontinuation due to adverse events in the CELEBREX
622 treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in
623 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo,
624 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

625

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

627

628

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

629

630

631

632

Gastrointestinal Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, stomatitis, tooth disorder, vomiting

633

634

635

Cardiovascular Aggravated hypertension, dry mouth, glaucoma, tenesmus

636

637

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

638

639

640

641

Resistance Mechanism Disorders Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media

642

643

644

Central, peripheral nervous system Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo

645

646

647

648

Female reproductive Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage,

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

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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, alkalinization 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:

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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

766 *Mfd. for Searle Ltd.*

767 *Caguas PR 00725*

768 *By Searle & Co.*

769 *San Juan PR 00936*

770

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.*

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781 *Skokie IL 60077*

782

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784

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786 **CELEBREX™**

787 (celecoxib capsules)

788

789

790 (A05264)

791

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