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2 **BEXTRA®**

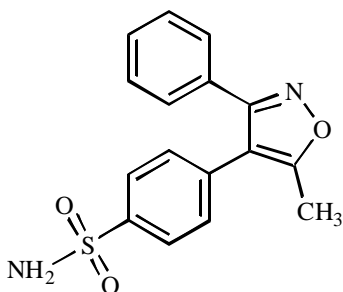
3 **valdecoxib tablets**

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5

6 **DESCRIPTION**

7 Valdecoxib is chemically designated as 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide and is
8 a diaryl substituted isoxazole. It has the following chemical structure:



9

Valdecoxib

10 The empirical formula for valdecoxib is C₁₆H₁₄N₂O₃S, and the molecular weight is 314.36. Valdecoxib
11 is a white crystalline powder that is relatively insoluble in water (10 µg/mL) at 25°C and pH 7.0, soluble in
12 methanol and ethanol, and freely soluble in organic solvents and alkaline (pH=12) aqueous solutions.

13 BEXTRA Tablets for oral administration contain either 10 mg or 20 mg of valdecoxib. Inactive
14 ingredients include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose
15 sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and
16 titanium dioxide.

17 **CLINICAL PHARMACOLOGY**

18 **Mechanism of Action**

19 Valdecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic
20 and antipyretic properties in animal models. The mechanism of action is believed to be due to inhibition of
21 prostaglandin synthesis primarily through inhibition of cyclooxygenase-2 (COX-2). At therapeutic plasma
22 concentrations in humans valdecoxib does not inhibit cyclooxygenase-1 (COX-1).

23 **Pharmacokinetics**24 **Absorption**

25 Valdecoxib achieves maximal plasma concentrations in approximately 3 hours. The absolute
26 bioavailability of valdecoxib is 83% following oral administration of BEXTRA compared to intravenous
27 infusion of valdecoxib.

28 Dose proportionality was demonstrated after single doses (1 - 400 mg) of valdecoxib. With multiple
29 doses (up to 100 mg/day for 14 days), valdecoxib exposure as measured by the AUC, increases in a
30 more than proportional manner at doses above 10 mg BID. Steady state plasma concentrations of
31 valdecoxib are achieved by day 4.

32 The steady state pharmacokinetic parameters of valdecoxib in healthy male subjects are shown in
33 Table 1.

34 **Table 1**

35 Mean (SD) Steady State Pharmacokinetic Parameters

Steady State Pharmacokinetic Parameters after Valdecoxib 10 mg Once Daily for 14 Days	Healthy Male Subjects (n=8, 20 to 42 yr.)
AUC _(0-24hr) (hr·ng/mL)	1479.0 (291.9)
C _{max} (ng/mL)	161.1 (48.1)
T _{max} (hr)	2.25 (0.71)
C _{min} (ng/mL)	21.9 (7.68)
Elimination Half-life (hr)	8.11 (1.32)

36 No clinically significant age or gender differences were seen in pharmacokinetic parameters that would
37 require dosage adjustments.

38 **Effect of Food and Antacid**

39 BEXTRA can be taken with or without food. Food had no significant effect on either the peak plasma
40 concentration (C_{max}) or extent of absorption (AUC) of valdecoxib when BEXTRA was taken with a high fat
41 meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1-2 hours. Administration
42 of BEXTRA with antacid (aluminum/magnesium hydroxide) had no significant effect on either the rate or
43 extent of absorption of valdecoxib.

44 **Distribution**

45 Plasma protein binding for valdecoxib is about 98% over the concentration range (21-2384 ng/mL).
46 Steady state apparent volume of distribution (V_{ss}/F) of valdecoxib is approximately 86 L after oral
47 administration. Valdecoxib and its active metabolite preferentially partition into erythrocytes with a blood
48 to plasma concentration ratio of about 2.5:1. This ratio remains approximately constant with time and
49 therapeutic blood concentrations.

50 Metabolism

51 In humans, valdecoxib undergoes extensive hepatic metabolism involving both P450 isoenzymes (3A4
52 and 2C9) and non-P450 dependent pathways (i.e., glucuronidation). Concomitant administration of
53 BEXTRA with known CYP 3A4 and 2C9 inhibitors (e.g., fluconazole and ketoconazole) can result in
54 increased plasma exposure of valdecoxib (see PRECAUTIONS — Drug Interactions).

55 One active metabolite of valdecoxib has been identified in human plasma at approximately 10% the
56 concentration of valdecoxib. This metabolite, which is a less potent COX-2 specific inhibitor than the
57 parent, also undergoes extensive metabolism and constitutes less than 2% of the valdecoxib dose
58 excreted in the urine and feces. Due to its low concentration in the systemic circulation, it is not likely to
59 contribute significantly to the efficacy profile of BEXTRA.

60 Excretion

61 Valdecoxib is eliminated predominantly via hepatic metabolism with less than 5% of the dose excreted
62 unchanged in the urine and feces. About 70% of the dose is excreted in the urine as metabolites, and
63 about 20% as valdecoxib N-glucuronide. The apparent oral clearance (CL/F) of valdecoxib is about 6
64 L/hr. The mean elimination half-life ($T_{1/2}$) ranges from 8-11 hours, and increases with age.

65 Special Populations**66 Geriatric**

67 In elderly subjects (> 65 years), weight-adjusted steady state plasma concentrations ($AUC_{(0-12hr)}$) are
68 about 30% higher than in young subjects. No dose adjustment is needed based on age.

69 Pediatric

70 BEXTRA has not been investigated in pediatric patients below 18 years of age.

71 Race

72 Pharmacokinetic differences due to race have not been identified in clinical and pharmacokinetic
73 studies conducted to date.

74 Hepatic Insufficiency

75 Valdecoxib plasma concentrations are significantly increased (130%) in patients with moderate (Child-
76 Pugh Class B) hepatic impairment. In clinical trials, doses of BEXTRA above those recommended have
77 been associated with fluid retention. Hence, treatment with BEXTRA should be initiated with caution in
78 patients with mild to moderate hepatic impairment and fluid retention. The use of BEXTRA in patients
79 with severe hepatic impairment (Child-Pugh Class C) is not recommended.

80 Renal Insufficiency

81 The pharmacokinetics of valdecoxib have been studied in patients with varying degrees of renal
82 impairment. Because renal elimination of valdecoxib is not important to its disposition, no clinically
83 significant changes in valdecoxib clearance were found even in patients with severe renal impairment or
84 in patients undergoing renal dialysis. In patients undergoing hemodialysis the plasma clearance (CL/F) of
85 valdecoxib was similar to the CL/F found in healthy elderly subjects (CL/F about 6 to 7 L/hr.) with normal
86 renal function (based on creatinine clearance).

87 NSAIDs have been associated with worsening renal function and use in advanced renal disease is not
88 recommended (see PRECAUTIONS – Renal Effects).

89 **Drug Interactions**

90 For quantitative information on the following drug interaction studies, see **PRECAUTIONS — Drug**
91 **Interactions.**

92 **General**

93 Valdecoxib undergoes both P450 (CYP) dependent and non-P450 dependent (glucuronidation)
94 metabolism. In vitro studies indicate that valdecoxib is not a significant inhibitor of CYP 1A2, 3A4, or 2D6
95 and is a weak inhibitor of CYP 2C9 and a weak to moderate inhibitor of CYP 2C19 at therapeutic
96 concentrations. The P450-mediated metabolic pathway of valdecoxib predominantly involves the 3A4
97 and 2C9 isozymes. Using prototype inhibitors and substrates of these isozymes, the following results
98 were obtained. Coadministration of a known inhibitor of CYP 2C9/3A4 (fluconazole) and a CYP 3A4
99 inhibitor (ketoconazole) enhanced the total plasma exposure (AUC) of valdecoxib. Coadministration of
100 valdecoxib with a CYP 3A4 inducer (phenytoin) decreased total plasma exposure (AUC) of valdecoxib.
101 (See PRECAUTIONS – Drug Interactions.)

102 Coadministration of valdecoxib with warfarin (a CYP 2C9 substrate) caused a small, but statistically
103 significant increase in plasma exposures of R-warfarin and S-warfarin, and also in the pharmacodynamic
104 effects (International Normalized Ratio - INR) of warfarin. (See PRECAUTIONS — Drug Interactions.)

105 Coadministration of valdecoxib with diazepam (a CYP 2C19/3A4 substrate) resulted in increased
106 exposure of diazepam, but not its major metabolite, desmethyldiazepam. (See PRECAUTIONS – Drug
107 Interactions.)

108 Coadministration of valdecoxib with glyburide (a CYP 2C9 substrate) (40 mg valdecoxib QD with 10 mg
109 glyburide BID) resulted in increased exposure of glyburide. (See PRECAUTIONS – Drug Interactions.)

110 Coadministration of valdecoxib with an oral contraceptive, 1 mg norethindrone/35 µg ethinyl estradiol
111 (CYP 3A4 substrates), resulted in increased exposure of both norethindrone and ethinyl estradiol. (See
112 PRECAUTIONS – Drug Interactions.)

113 Coadministration of valdecoxib with omeprazole (a CYP 3A4/2C19 substrate) caused an increase in
114 omeprazole exposure. (See PRECAUTIONS – Drug Interactions.)

115 Coadministration of valdecoxib with dextromethorphan (a CYP 2D6/3A4 substrate) resulted in an
116 increase in dextromethorphan plasma levels above those seen in subjects with normal levels of CYP
117 2D6. Even so these levels were almost 5-fold lower than those seen in CYP 2D6 poor metabolizers (See
118 PRECAUTIONS – Drug Interactions.)

119 Coadministration of valdecoxib with phenytoin (a CYP 2C9/2C19 substrate) did not affect the
120 pharmacokinetics of phenytoin.

121 Coadministration of valdecoxib, or its injectable prodrug, with substrates of CYP 2C9 (propofol) and
122 CYP 3A4 (midazolam, alfentanil, fentanyl) did not inhibit the metabolism of these substrates.

123 **CLINICAL STUDIES**

124 The efficacy and clinical utility of BEXTRA Tablets have been demonstrated in osteoarthritis (OA),
 125 rheumatoid arthritis (RA) and in the treatment of primary dysmenorrhea.

126 **Osteoarthritis**

127 BEXTRA was evaluated for treatment of the signs and symptoms of osteoarthritis of the knee or hip, in
 128 five double-blind, randomized, controlled trials in which 3918 patients were treated for 3 to 6 months.
 129 BEXTRA was shown to be superior to placebo in improvement in three domains of OA symptoms: (1) the
 130 WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness
 131 and functional measures in OA, (2) the overall patient assessment of pain, and (3) the overall patient
 132 global assessment. The two 3-month pivotal trials in OA generally showed changes statistically
 133 significantly different from placebo, and comparable to the naproxen control, in measures of these
 134 domains for the 10 mg/day dose. No additional benefit was seen with a valdecoxib 20-mg daily dose.

135 **Rheumatoid Arthritis**

136 BEXTRA demonstrated significant reduction compared to placebo in the signs and symptoms of RA, as
 137 measured by the ACR (American College of Rheumatology) 20 improvement, a composite defined as
 138 both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement
 139 in three of the following five: patient global, physician global, patient pain, patient function assessment,
 140 and C-reactive protein (CRP). BEXTRA was evaluated for treatment of the signs and symptoms of
 141 rheumatoid arthritis in four double-blind, randomized, controlled studies in which 3444 patients were
 142 treated for 3 to 6 months. The two 3-month pivotal trials compared valdecoxib to naproxen and placebo.
 143 The results for the ACR20 responses in these trials are shown below (Table 2). Trials of BEXTRA in
 144 rheumatoid arthritis allowed concomitant use of corticosteroids and/or disease-modifying anti-rheumatic
 145 drugs (DMARDs), such as methotrexate, gold salts, and hydroxychloroquine. No additional benefit was
 146 seen with a valdecoxib 20-mg daily dose.

147

148

149

Table 2

ACR20 Response Rate (%) in Rheumatoid Arthritis

	Study 1		Study 2	
BEXTRA 10 mg/day	49%**	(103/209)	46%**	(103/226)
BEXTRA 20 mg/day	48%**	(102/212)	47%*	(103/219)
Naproxen 500 mg BID	44%*	(100/225)	53%**	(115/219)
Placebo	32%	(70/222)	32%	(71/220)

150

* p<0.01; ** p< 0.001 compared to placebo

151 **Primary Dysmenorrhea**

152 BEXTRA was compared to naproxen sodium 550 mg in two placebo-controlled studies of women with
 153 moderate to severe primary dysmenorrhea. The onset of analgesia was within 60 minutes for BEXTRA
 154 20 mg. The onset, magnitude, and duration of analgesic effect with BEXTRA 20 mg were comparable to
 155 naproxen sodium 550 mg.

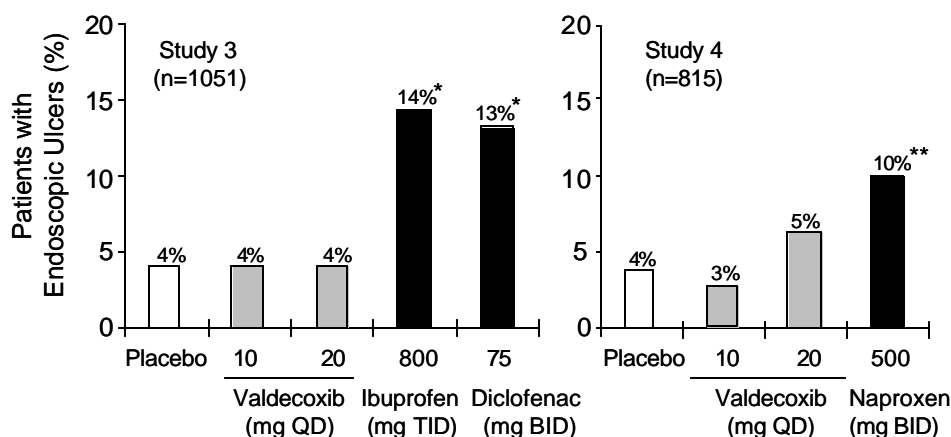
156 **Safety Studies**

157 **Gastrointestinal (GI) Endoscopy Studies with Therapeutic Doses:** Scheduled upper GI endoscopic
 158 evaluations were performed with BEXTRA at doses of 10 and 20 mg daily in over 800 OA patients who
 159 were enrolled into two randomized 3-month studies using active comparators and placebo controls (Study
 160 3 and Study 4). These studies enrolled patients free of endoscopic ulcers at baseline and compared rates
 161 of endoscopic ulcers, defined as any gastroduodenal ulcer seen endoscopically provided it was of
 162 “unequivocal depth” and at least 3 mm in diameter.

163 In both studies, BEXTRA 10 mg daily was associated with a statistically significant lower incidence of
 164 endoscopic gastroduodenal ulcers over the study period compared to the active comparators. Figure 1
 165 summarizes the incidence of gastroduodenal ulcers in Studies 3 and 4 for the placebo, valdecoxib, and
 166 active control arms.

167 **Figure 1**

168 Incidence of Endoscopically Observed
 169 Gastroduodenal Ulcers in OA Patients



* Significantly different vs placebo and both valdecoxib treatment groups; p<0.05

** Significantly different vs placebo and valdecoxib 10 mg; p<0.05

170 **Safety Study with Supratherapeutic Doses:** Scheduled upper GI endoscopic evaluations were
 171 performed in a randomized 6-month study of 1217 patients with OA and RA comparing valdecoxib 20 mg
 172 BID (40 mg daily) and 40 mg BID (80 mg daily) (4 to 8 times the recommended therapeutic dose) to
 173 naproxen 500 mg BID (Study 5). This study also formally assessed renal events as a primary outcome
 174 with supratherapeutic doses of BEXTRA. The renal endpoint was defined as any of the following:
 175 new/increase in edema, new/increase in congestive heart failure, increase in blood pressure (BP; >20
 176 mm Hg systolic, >10 mm Hg diastolic), new/increase in BP treatment, new/increase in diuretic therapy,

177 creatinine increase over 30% (or >1.2 mg/dL if baseline <0.9 mg/dL), BUN increase over 200% or >50
 178 mg/dL, 24-hr urinary protein increase to >500 mg (if baseline 0-150 mg or >750 if baseline 151-300 or
 179 >1000 if baseline 301-500), serum potassium increase to >6 mEq/L, or serum sodium decrease to <130
 180 mEq/L.

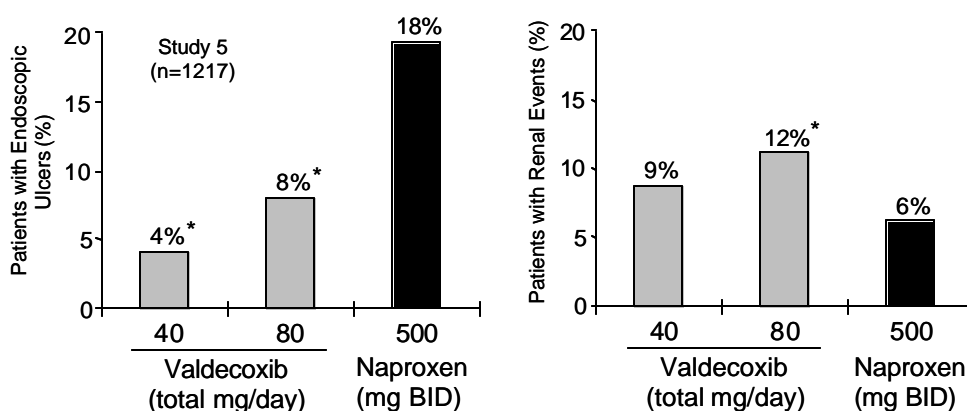
181 Figure 2 summarizes the incidence rates of gastroduodenal ulcers and renal events that were
 182 seen in Study 5. BEXTRA 40 mg daily and 80 mg daily were associated with a statistically significant
 183 lower incidence of endoscopic gastroduodenal ulcers over the study period compared to naproxen.
 184 The incidence of renal events was significantly different between the BEXTRA 80 mg daily group and
 185 naproxen. The clinical relevance of renal events observed with supratherapeutic doses (4 to 8 times
 186 the recommended therapeutic dose) of BEXTRA is not known (see PRECAUTIONS – Renal Effects).

187

Figure 2

188

Incidence of Endoscopic Gastroduodenal Ulcers and



* Significantly different vs naproxen, p<0.05

189

Renal Events in the High-dose Safety Study

190 **Renal Safety at the Therapeutic Chronic Dose:** The renal effects of valdecoxib compared with placebo
 191 and conventional NSAIDs were also assessed by prospectively designed pooled analyses of renal events
 192 data (see definition above — Supratherapeutic Doses) from five placebo- and active-controlled 12-week
 193 arthritis trials that included 995 OA or RA patients given valdecoxib 10 mg daily. The incidence of renal
 194 events observed in this analysis with valdecoxib 10 mg daily (3%), ibuprofen 800 mg TID (7%), naproxen
 195 500 mg BID (2%) and diclofenac 75 mg BID (4%) were significantly higher than placebo-treated patients
 196 (1%). In all treatment groups, the majority of renal events were either due to the occurrence of edema or
 197 worsening BP.

198 **Gastrointestinal Ulcers in High-Risk Patients:** Subset analyses were performed of patients with risk
 199 factors (age, concomitant low-dose aspirin use, history of prior ulcer disease) enrolled in four upper GI
 200 endoscopic studies. Table 3 summarizes the trends seen.

201
202
203

Table 3
Incidence of Endoscopic Gastroduodenal Ulcers
in Patients With and Without Selected Risk Factors

Risk Factor	Placebo-controlled Studies		Active-controlled Studies			
	Placebo	Valdecoxib (10-20 mg daily)	Valdecoxib (10-80 mg daily)	Ibuprofen 800 mg TID	Naproxen 500 mg BID	Diclofenac 75 mg BID
Age						
<65 yrs	3.7% (8/219)	3.5% (17/484)	3.7%	8.2% (9/110)	12.8% (51/397)	13.2% (34/258)
≥65 yrs	5.8% (8/137)	4.6% (12/262)	(48/1306)7.6% (43/568)	21.6% (16/74)	22.0% (33/150)	18.2% (25/137)
Concomitant Low Dose Aspirin Use						
no	4.4% (13/298)	3.2% (21/650)	3.8% (64/1671)	9.8% (15/153)	16.0% (75/468)	12.8% (45/351)
yes	5.2% (3/58)	8.3% (8/96)	13.3% (27/203)	32.3% (10/31)	11.4% (9/79)	31.8% (14/44)
History of Ulcer Disease						
no	4.4% (14/317)	3.4% (22/647)	4.1% (68/1666)	13.8% (22/160)	13.3% (63/475)	14.7% (52/354)
yes	5.1% (2/39)	7.1% (7/99)	11.1% (23/208)	12.5% (3/24)	29.2% (21/72)	17.1% (7/41)

204 No statistical conclusions can be drawn from these comparisons.

205 The correlation between findings of endoscopic studies, and the incidence of clinically significant
206 serious upper GI events has not been established.207 **Platelets:** In four clinical studies with young and elderly (≥65 years) subjects, single and multiple doses
208 up to 7 days of BEXTRA 10 to 40 mg BID had no effect on platelet aggregation.209 **INDICATIONS AND USAGE**

210 BEXTRA Tablets are indicated:

- 211
- For relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis.
 - For the treatment of primary dysmenorrhea.
- 212

213 **CONTRAINDICATIONS**214 BEXTRA should not be given to patients who have demonstrated allergic-type reactions to
215 sulfonamides. BEXTRA Tablets are contraindicated in patients with known hypersensitivity to valdecoxib.
216 BEXTRA should not be given to patients who have experienced asthma, urticaria, or allergic-type
217 reactions after taking aspirin or NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs are
218 possible in such patients (see WARNINGS — Anaphylactoid Reactions, and PRECAUTIONS —
219 Preexisting Asthma).

220 WARNINGS**221 Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation**

222 Serious gastrointestinal toxicity such as bleeding, ulceration and perforation of the stomach, small
223 intestine or large intestine can occur at any time with or without warning symptoms in patients treated with
224 nonsteroidal anti-inflammatory drugs (NSAIDs). Minor gastrointestinal problems such as dyspepsia are
225 common and may also occur at any time during NSAID therapy. Therefore, physicians and patients
226 should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms.
227 Patients should be informed about the signs and symptoms of serious GI toxicity and the steps to take if
228 they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been
229 adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID
230 therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation
231 caused by NSAIDs appear to occur in approximately 1% of patients treated for 3 to 6 months and 2-4% of
232 patients treated for one year. These trends continue, thus increasing the likelihood of developing a
233 serious GI event at some time during the course of therapy. However, even short-term therapy is not
234 without risk.

235 NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or
236 gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients
237 and therefore special care should be taken in treating this population. For high risk patients, alternate
238 therapies that do not involve NSAIDs should be considered.

239 Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal*
240 *bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than
241 patients with neither of these risk factors. In addition to a past history of ulcer disease,
242 pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that
243 may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with
244 anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general
245 health status. (See CLINICAL STUDIES — Safety Studies.)

246 Serious Skin Reactions

247 Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic
248 epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving
249 BEXTRA (see ADVERSE REACTIONS-Postmarketing Experience). Fatalities due to Stevens-Johnson
250 syndrome and toxic epidermal necrolysis have been reported. BEXTRA should be discontinued at the
251 first appearance of skin rash or any other sign of hypersensitivity.

252 Anaphylactoid Reactions

253 In postmarketing experience, cases of hypersensitivity reactions (anaphylactic reactions and
254 angioedema) have been reported in patients receiving BEXTRA (see ADVERSE REACTIONS-
255 Postmarketing Experience). These cases have occurred in patients with and without a history of allergic-

256 type reactions to sulfonamides (see CONTRAINDICATIONS). BEXTRA should not be given to patients
257 with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience
258 rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking
259 aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS — Pre-existing Asthma).
260 Emergency help should be sought in cases where an anaphylactoid reaction occurs.

261 **Advanced Renal Disease**

262 No information is available regarding the safe use of BEXTRA Tablets in patients with advanced kidney
263 disease. Therefore, treatment with BEXTRA is not recommended in these patients. If therapy with
264 BEXTRA must be initiated, close monitoring of the patient's kidney function is advisable (see
265 PRECAUTIONS — Renal Effects).

266 **Pregnancy**

267 In late pregnancy, BEXTRA should be avoided because it may cause premature closure of the ductus
268 arteriosus.

269 **PRECAUTIONS**

270 **General**

271 BEXTRA Tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid
272 insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-
273 responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly
274 if a decision is made to discontinue corticosteroids.

275 The pharmacological activity of valdecoxib in reducing fever and inflammation may diminish the utility
276 of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

277 **Hepatic Effects**

278 Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs.
279 Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have
280 been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory
281 abnormalities may progress, may remain unchanged, or may remain transient with continuing therapy.
282 Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and
283 hepatic failure (some with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of
284 valdecoxib, the incidence of borderline (defined as 1.2- to 3.0-fold) elevations of liver tests was 8.0% for
285 valdecoxib and 8.4% for placebo, while approximately 0.3% of patients taking valdecoxib, and 0.2% of
286 patients taking placebo, had notable (defined as greater than 3-fold) elevations of ALT or AST.

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

291 Renal Effects

292 Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.
293 Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in
294 the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory
295 drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood
296 flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are
297 those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and Angiotensin
298 Converting Enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually
299 followed by recovery to the pretreatment state.

300 Caution should be used when initiating treatment with BEXTRA in patients with considerable
301 dehydration. It is advisable to rehydrate patients first and then start therapy with BEXTRA. Caution is
302 also recommended in patients with preexisting kidney disease. (See WARNINGS — Advanced Renal
303 Disease.)

304 Hematological Effects

305 Anemia is sometimes seen in patients receiving BEXTRA. Patients on long-term treatment with
306 BEXTRA should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of
307 anemia.

308 BEXTRA does not generally affect platelet counts, prothrombin time (PT), or activated partial
309 thromboplastin time (APTT), and does not appear to inhibit platelet aggregation at indicated dosages
310 (See CLINICAL STUDIES — Safety Studies — Platelets).

311 Fluid Retention and Edema

312 Fluid retention and edema have been observed in some patients taking BEXTRA (see ADVERSE
313 REACTIONS). Therefore, BEXTRA should be used with caution in patients with fluid retention,
314 hypertension, or heart failure.

315 Preexisting Asthma

316 Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-
317 sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross
318 reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has
319 been reported in such aspirin-sensitive patients, BEXTRA should not be administered to patients with this
320 form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

321 Information for Patients

322 BEXTRA can cause GI discomfort and, rarely, more serious GI side effects, which may result in
323 hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur
324 without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and
325 bleeding, and should ask for medical advice when observing any indicative sign or symptoms. Patients
326 should be apprised of the importance of this follow-up (see WARNINGS — Gastrointestinal (GI) Effects —
327 Risk of GI Ulceration, Bleeding, and Perforation).

328 Patients should report to their physicians, signs or symptoms of gastrointestinal ulceration or bleeding,
329 skin rash, weight gain, or edema.

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

333 Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid
334 reaction (see WARNINGS — Anaphylactoid Reactions).

335 In late pregnancy, BEXTRA should be avoided because it may cause premature closure of the ductus
336 arteriosus.

337 **Laboratory Tests**

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

340 **Drug Interactions**

341 The drug interaction studies with valdecoxib were performed both with valdecoxib and a rapidly
342 hydrolyzed intravenous prodrug form. The results from trials using the intravenous prodrug are reported in
343 this section as they relate to the role of valdecoxib in drug interactions.

344 **General:** In humans, valdecoxib metabolism is predominantly mediated via CYP 3A4 and 2C9 with
345 glucuronidation being a further (20%) route of metabolism. In vitro studies indicate that valdecoxib is a
346 moderate inhibitor of CYP 2C19 (IC₅₀ = 6 µg/mL or 19 µM) and 2C9 (IC₅₀ = 13 µg/mL or 41 µM), and a
347 weak inhibitor of CYP 2D6 (IC₅₀ = 31 µg/mL or 100 µM) and 3A4 (IC₅₀ = 44 µg/mL or 141 µM)..

348 **Aspirin:** Concomitant administration of aspirin with valdecoxib may result in an increased risk of GI
349 ulceration and complications compared to valdecoxib alone. Because of its lack of anti-platelet effect
350 valdecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

351 In a parallel group drug interaction study comparing the intravenous prodrug form of valdecoxib at 40
352 mg BID (n=10) vs placebo (n=9), valdecoxib had no effect on in vitro aspirin-mediated inhibition of
353 arachidonate- or collagen-stimulated platelet aggregation.

354 **Methotrexate:** Valdecoxib 10 mg BID did not show a significant effect on the plasma exposure or renal
355 clearance of methotrexate.

356 **ACE-inhibitors:** Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-
357 inhibitors. This interaction should be given consideration in patients taking BEXTRA concomitantly with
358 ACE-inhibitors.

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

362 **Anticonvulsants (Phenytoin):** Steady state plasma exposure (AUC) of valdecoxib (40 mg BID for 12
363 days) was decreased by 27% when co-administered with multiple doses (300 mg QD for 12 days) of
364 phenytoin (a CYP 3A4 inducer). Patients already stabilized on valdecoxib should be closely monitored

365 for loss of symptom control with phenytoin coadministration. Valdecoxib did not have a statistically
366 significant effect on the pharmacokinetics of phenytoin (a CYP 2C9 and CYP 2C19 substrate).

367 Drug interaction studies with other anticonvulsants have not been conducted. Routine monitoring
368 should be performed when therapy with BEXTRA is either initiated or discontinued in patients on
369 anticonvulsant therapy.

370 **Dextromethorphan:** Dextromethorphan is primarily metabolized by CYP 2D6 and to a lesser extent by
371 3A4. Coadministration with valdecoxib (40 mg BID for 7 days) resulted in a significant increase in
372 dextromethorphan plasma levels suggesting that, at these doses, valdecoxib is a weak inhibitor of 2D6.
373 Even so dextromethorphan plasma concentrations in the presence of high doses of valdecoxib were
374 almost 5-fold lower than those seen in CYP 2D6 poor metabolizers suggesting that dose adjustment is
375 not necessary.

376 **Lithium:** Valdecoxib 40 mg BID for 7 days produced significant decreases in lithium serum clearance
377 (25%) and renal clearance (30%) with a 34% higher serum exposure compared to lithium alone. Lithium
378 serum concentrations should be monitored closely when initiating or changing therapy with BEXTRA in
379 patients receiving lithium. Lithium carbonate (450 mg BID for 7 days) had no effect on valdecoxib
380 pharmacokinetics.

381 **Warfarin:** The effect of valdecoxib on the anticoagulant effect of warfarin (1 - 8 mg/day) was studied in
382 healthy subjects by coadministration of BEXTRA 40 mg BID for 7 days. Valdecoxib caused a statistically
383 significant increase in plasma exposures of R-warfarin and S-warfarin (12% and 15%, respectively), and
384 in the pharmacodynamic effects (prothrombin time, measured as INR) of warfarin. While mean INR
385 values were only slightly increased with coadministration of valdecoxib, the day-to-day variability in
386 individual INR values was increased. Anticoagulant therapy should be monitored, particularly during the
387 first few weeks, after initiating therapy with BEXTRA in patients receiving warfarin or similar agents.

388 **Fluconazole and Ketoconazole:** Ketoconazole and fluconazole are predominantly CYP 3A4 and 2C9
389 inhibitors, respectively. Concomitant single dose administration of valdecoxib 20 mg with multiple doses
390 of ketoconazole and fluconazole produced a significant increase in exposure of valdecoxib. Plasma
391 exposure (AUC) to valdecoxib was increased 62% when coadministered with fluconazole and 38% when
392 coadministered with ketoconazole.

393 **Glyburide:** Glyburide is a CYP 2C9 substrate. Coadministration of valdecoxib (10 mg BID for 7 days)
394 with glyburide (5 mg QD or 10 mg BID) did not affect the pharmacokinetics (exposure) of glyburide.
395 Coadministration of valdecoxib (40 mg BID (day 1) and 40 mg QD (days 2-7)) with glyburide (5 mg QD)
396 did not affect either the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and
397 insulin levels) of glyburide. Coadministration of valdecoxib (40 mg BID (day 1) and 40 mg QD (days 2-7))
398 with glyburide (10 mg glyburide BID) resulted in 21% increase in glyburide AUC₀₋₁₂ and a 16% increase in
399 glyburide C_{max} leading to a 16% decrease in glucose AUC₀₋₂₄. Insulin parameters were not affected.
400 Because changes in glucose concentrations with valdecoxib coadministration were within the normal
401 variability and individual glucose concentrations were above or near 70 mg/dL, dose adjustment for

402 glyburide (5 mg QD and 10 mg BID) with valdecoxib coadministration (up to 40 mg QD) is not indicated.
403 Coadministration of glyburide with doses higher than 40 mg valdecoxib (e.g., 40 mg BID) have not been
404 studied.

405 **Omeprazole:** Omeprazole is a CYP 3A4 substrate and CYP 2C19 substrate and inhibitor. Valdecoxib
406 steady state plasma concentrations (40 mg BID) were not affected significantly with multiple doses of
407 omeprazole (40 mg QD). Coadministration with valdecoxib increased exposure of omeprazole (AUC) by
408 46%. Drugs whose absorption is sensitive to pH may be negatively impacted by concomitant
409 administration of omeprazole and valdecoxib. However, because higher doses (up to 360 mg QD) of
410 omeprazole are tolerated in Zollinger-Ellison (ZE) patients, no dose adjustment for omeprazole is
411 recommended at current doses. Coadministration of valdecoxib with doses higher than 40 mg QD
412 omeprazole has not been studied.

413 **Oral Contraceptives:** Valdecoxib (40 mg BID) did not induce the metabolism of the combination oral
414 contraceptive norethindrone/ethinyl estradiol (1 mg /35 mcg combination, Ortho-Novum 1/35[®]).
415 Coadministration of valdecoxib and Ortho-Novum 1/35[®] increased the exposure of norethindrone and ethinyl
416 estradiol by 20% and 34%, respectively. Although there is little risk for loss of contraceptive efficacy, the
417 clinical significance of these increased exposures in terms of safety is not known. These increased
418 exposures of norethindrone and ethinyl estradiol should be taken into consideration when selecting an oral
419 contraceptive for women taking valdecoxib.

420 **Diazepam:** Diazepam (Valium) is a CYP 3A4 and CYP 2C19 substrate. Plasma exposure of diazepam
421 (10 mg BID) was increased by 28% following administration of valdecoxib (40 mg BID) for 12 days, while
422 plasma exposure of valdecoxib (40 mg BID) was not substantially increased following administration of
423 diazepam (10 mg BID) for 12 days. Although the magnitude of changes in diazepam plasma exposure
424 when coadministered with valdecoxib were not sufficient to warrant dosage adjustments, patients may
425 experience enhanced sedative side effects caused by increased exposure of diazepam under this
426 circumstance. Patients should be cautioned against engaging in hazardous activities requiring complete
427 mental alertness such as operating machinery or driving a motor vehicle.

428 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

429 Valdecoxib was not carcinogenic in rats given oral doses up to 7.5 mg/kg/day for males and
430 1.5 mg/kg/day for females (equivalent to approximately 2- to 6-fold human exposure at 20 mg QD as
431 measured by the AUC_(0-24hr)) or in mice given oral doses up to 25 mg/kg/day for males and 50 mg/kg/day
432 for females (equivalent to approximately 0.6- to 2.4-fold human exposure at 20 mg QD as measured by
433 the AUC_(0-24hr)) for two years.

434 Valdecoxib was not mutagenic in an Ames test or a mutation assay in Chinese hamster ovary (CHO)
435 cells, nor was it clastogenic in a chromosome aberration assay in CHO cells or in an *in vivo* micronucleus
436 test in rat bone marrow.

437 Valdecoxib did not impair male rat fertility at oral doses up to 9.0 mg/kg/day (equivalent to
438 approximately 3- to 6-fold human exposure at 20 mg QD as measured by the AUC_(0-24hr)). In female rats,

439 a decrease in ovulation with increased pre- and post-implantation loss resulted in decreased live
440 embryos/fetuses at doses ≥ 2 mg/kg/day (equivalent to approximately 2-fold human exposure at 20 mg
441 QD as measured by the $AUC_{(0-24hr)}$ for valdecoxib). The effects on female fertility were reversible. This
442 effect is expected with inhibition of prostaglandin synthesis and is not the result of irreversible alteration of
443 female reproductive function.

444 **Pregnancy**

445 **Teratogenic Effects:** Pregnancy Category C.

446 The incidence of fetuses with skeletal anomalies such as semi-bipartite thoracic vertebra centra and
447 fused sternbrae was slightly higher in rabbits at an oral dose of 40 mg/kg/day (equivalent to
448 approximately 72-fold human exposures at 20 mg QD as measured by the $AUC_{(0-24hr)}$) throughout
449 organogenesis. Valdecoxib was not teratogenic in rabbits up to an oral dose of 10 mg/kg/day (equivalent
450 to approximately 8-fold human exposures at 20 mg QD as measured by the $AUC_{(0-24hr)}$).

451 Valdecoxib was not teratogenic in rats up to an oral dose of 10 mg/kg/day (equivalent to approximately
452 19-fold human exposure at 20 mg QD as measured by the $AUC_{(0-24hr)}$). There are no studies in pregnant
453 women. However, valdecoxib crosses the placenta in rats and rabbits. BEXTRA should be used during
454 pregnancy only if the potential benefit justifies the potential risk to the fetus.

455 **Non-Teratogenic Effects:** Valdecoxib caused increased pre-and post-implantation loss with reduced
456 live fetuses at oral doses ≥ 10 mg/kg/day (equivalent to approximately 19-fold human exposure at 20 mg
457 QD as measured by the $AUC_{(0-24hr)}$) in rats and an oral dose of 40 mg/kg/day (equivalent to approximately
458 72-fold human exposure at 20 mg QD as measured by the $AUC_{(0-24hr)}$) in rabbits throughout
459 organogenesis. In addition, reduced neonatal survival and decreased neonatal body weight when rats
460 were treated with valdecoxib at oral doses ≥ 6 mg/kg/day (equivalent to approximately 7-fold human
461 exposure at 20 mg QD as measured by the $AUC_{(0-24hr)}$) throughout organogenesis and lactation period.
462 No studies have been conducted to evaluate the effect of valdecoxib on the closure of the ductus
463 arteriosus in humans. Therefore, as with other drugs known to inhibit prostaglandin synthesis, use of
464 BEXTRA during the third trimester of pregnancy should be avoided.

465 **Labor and Delivery**

466 Valdecoxib produced no evidence of delayed labor or parturition at oral doses up to 10 mg/kg/day in
467 rats (equivalent to approximately 19-fold human exposure at 20 mg QD as measured by the $AUC_{(0-24hr)}$).
468 The effects of BEXTRA on labor and delivery in pregnant women are unknown.

469 **Nursing Mothers**

470 Valdecoxib and its active metabolite are excreted in the milk of lactating rats. It is not known whether
471 this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of
472 the potential for adverse reactions in nursing infants from BEXTRA, a decision should be made whether
473 to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the
474 mother and the importance of nursing to the infant.

475 **Pediatric Use**

476 Safety and effectiveness of BEXTRA in pediatric patients below the age of 18 years have not been
477 evaluated.

478 **Geriatric Use**

479 Of the patients who received BEXTRA in arthritis clinical trials of three months duration, or greater,
480 approximately 2100 were 65 years of age or older, including 570 patients who were 75 years or older. No
481 overall differences in effectiveness were observed between these patients and younger patients.

482 **ADVERSE REACTIONS**

483 Of the patients treated with BEXTRA Tablets in controlled arthritis trials, 2665 were patients with OA,
484 and 2684 were patients with RA. More than 4000 patients have received a chronic total daily dose of
485 BEXTRA 10 mg or more. More than 2800 patients have received BEXTRA 10 mg/day, or more, for at
486 least 6 months and 988 of these have received BEXTRA for at least 1 year.

487 **Osteoarthritis and Rheumatoid Arthritis**

488 Table 4 lists all adverse events, regardless of causality, that occurred in $\geq 2.0\%$ of patients receiving
489 BEXTRA 10 and 20 mg/day in studies of three months or longer from 7 controlled studies conducted in
490 patients with OA or RA that included a placebo and/or a positive control group.

491
492
493

Table 4
Adverse Events with Incidence \geq 2.0% in Valdecoxib Treatment Groups:
Controlled Arthritis Trials of Three Months or Longer

Adverse Event	Placebo	(Total Daily Dose)				Naproxen 1000 mg
		Valdecoxib 10 mg	Valdecoxib 20 mg	Diclofenac 150 mg	Ibuprofen 2400 mg	
Number Treated	973	1214	1358	711	207	766
<i>Autonomic Nervous System Disorders</i>						
Hypertension	0.6	1.6	2.1	2.5	2.4	1.7
<i>Body as a Whole</i>						
Back pain	1.6	1.6	2.7	2.8	1.4	1.0
Edema peripheral	0.7	2.4	3.0	3.2	2.9	2.1
Influenza-like symptoms	2.2	2.0	2.2	3.1	2.9	2.0
Injury accidental	2.8	4.0	3.7	3.9	3.9	3.0
<i>Central and Peripheral Nervous System Disorders</i>						
Dizziness	2.1	2.6	2.7	4.2	3.4	2.7
Headache	7.1	4.8	8.5	6.6	4.3	5.5
<i>Gastrointestinal System Disorders</i>						
Abdominal fullness	2.0	2.1	1.9	3.0	2.9	2.5
Abdominal pain	6.3	7.0	8.2	17.0	8.2	10.1
Diarrhea	4.2	5.4	6.0	10.8	3.9	4.7
Dyspepsia	6.3	7.9	8.7	13.4	15.0	12.9
Flatulence	4.1	2.9	3.5	3.1	7.7	5.4
Nausea	5.9	7.0	6.3	8.4	7.7	8.7
<i>Musculoskeletal System Disorders</i>						
Myalgia	1.6	2.0	1.9	2.4	2.4	1.4
<i>Respiratory System Disorders</i>						
Sinusitis	2.2	2.6	1.8	1.1	3.4	3.4
Upper respiratory tract infection	6.0	6.7	5.7	6.3	4.3	6.4
<i>Skin and Appendages Disorders</i>						
Rash	1.0	1.4	2.1	1.5	0.5	1.4

494 In these placebo- and active-controlled clinical trials, the discontinuation rate due to adverse events
495 was 7.5% for arthritis patients receiving valdecoxib 10 mg daily, 7.9% for arthritis patients receiving
496 valdecoxib 20 mg daily and 6.0% for patients receiving placebo.

497 In the seven controlled OA and RA studies, the following adverse events occurred in 0.1 - 1.9% of
498 patients treated with BEXTRA 10 – 20 mg daily, regardless of causality.

499 **Application site disorders:** Cellulitis, dermatitis contact
500 **Cardiovascular:** Aggravated hypertension, aneurysm, angina pectoris, arrhythmia, cardiomyopathy,
501 congestive heart failure, coronary artery disorder, heart murmur, hypotension
502 **Central, peripheral nervous system:** Cerebrovascular disorder, hypertonia, hypoesthesia, migraine,
503 neuralgia, neuropathy, paresthesia, tremor, twitching, vertigo
504 **Endocrine:** Goiter
505 **Female reproductive:** Amenorrhea, dysmenorrhea, leukorrhea, mastitis, menstrual disorder,
506 menorrhagia, menstrual bloating, vaginal hemorrhage
507 **Gastrointestinal:** Abnormal stools, constipation, diverticulosis, dry mouth, duodenal ulcer, duodenitis,
508 eructation, esophagitis, fecal incontinence, gastric ulcer, gastritis, gastroenteritis, gastroesophageal
509 reflux, hematemesis, hematochezia, hemorrhoids, hemorrhoids bleeding, hiatal hernia, melena,
510 stomatitis, stool frequency increased, tenesmus, tooth disorder, vomiting
511 **General:** Allergy aggravated, allergic reaction, asthenia, chest pain, chills, cyst NOS, edema generalized,
512 face edema, fatigue, fever, hot flushes, halitosis, malaise, pain, periorbital swelling, peripheral pain
513 **Hearing and vestibular:** Ear abnormality, earache, tinnitus
514 **Heart rate and rhythm:** Bradycardia, palpitation, tachycardia
515 **Hemic:** Anemia
516 **Liver and biliary system:** Hepatic function abnormal, hepatitis, ALT increased, AST increased
517 **Male reproductive:** Impotence, prostatic disorder
518 **Metabolic and nutritional:** Alkaline phosphatase increased, BUN increased, CPK increased, creatinine
519 increased, diabetes mellitus, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperkalemia,
520 hyperlipemia, hyperuricemia, hypocalcemia, hypokalemia, LDH increased, thirst increased, weight
521 decrease, weight increase, xerophthalmia
522 **Musculoskeletal:** Arthralgia, fracture accidental, neck stiffness, osteoporosis, synovitis, tendonitis
523 **Neoplasm:** Breast neoplasm, lipoma, malignant ovarian cyst
524 **Platelets (bleeding or clotting):** Ecchymosis, epistaxis, hematoma NOS, thrombocytopenia
525 **Psychiatric:** Anorexia, anxiety, appetite increased, confusion, depression, depression aggravated,
526 insomnia, nervousness, morbid dreaming, somnolence
527 **Resistance mechanism disorders:** Herpes simplex, herpes zoster, infection fungal, infection soft tissue,
528 infection viral, moniliasis, moniliasis genital, otitis media
529 **Respiratory:** Abnormal breath sounds, bronchitis, bronchospasm, coughing, dyspnea, emphysema,
530 laryngitis, pneumonia, pharyngitis, pleurisy, rhinitis
531 **Skin and appendages:** Acne, alopecia, dermatitis, dermatitis fungal, eczema, photosensitivity allergic
532 reaction, pruritus, rash erythematous, rash maculopapular, rash psoriaform, skin dry, skin hypertrophy,
533 skin ulceration, sweating increased, urticaria
534 **Special senses:** Taste perversion

- 535 **Urinary system:** Albuminuria, cystitis, dysuria, hematuria, micturition frequency increased, pyuria, urinary
536 incontinence, urinary tract infection
- 537 **Vascular:** Claudication intermittent, hemangioma acquired, varicose vein
- 538 **Vision:** Blurred vision, cataract, conjunctival hemorrhage, conjunctivitis, eye pain, keratitis, vision
539 abnormal
- 540 **White cell and RES disorders:** Eosinophilia, leukopenia, leukocytosis, lymphadenopathy, lymphangitis,
541 lymphopenia
- 542 Other serious adverse events that were reported rarely (estimated <0.1%) in clinical trials, regardless of
543 causality, in patients taking BEXTRA:
- 544 **Autonomic nervous system disorders:** Hypertensive encephalopathy, vasospasm
- 545 **Cardiovascular:** Abnormal ECG, aortic stenosis, atrial fibrillation, carotid stenosis, coronary thrombosis,
546 heart block, heart valve disorders, mitral insufficiency, myocardial infarction, myocardial ischemia,
547 pericarditis, syncope, thrombophlebitis, unstable angina, ventricular fibrillation
- 548 **Central, peripheral nervous system:** Convulsions
- 549 **Endocrine:** Hyperparathyroidism
- 550 **Female reproductive:** Cervical dysplasia
- 551 **Gastrointestinal:** Appendicitis, colitis with bleeding, dysphagia, esophageal perforation, gastrointestinal
552 bleeding, ileus, intestinal obstruction, peritonitis
- 553 **Hemic:** Lymphoma-like disorder, pancytopenia
- 554 **Liver and biliary system:** Cholelithiasis
- 555 **Metabolic:** Dehydration
- 556 **Musculoskeletal:** Pathological fracture, osteomyelitis
- 557 **Neoplasm:** Benign brain neoplasm, bladder carcinoma, carcinoma, gastric carcinoma, prostate
558 carcinoma, pulmonary carcinoma
- 559 **Platelets (bleeding or clotting):** Embolism, pulmonary embolism, thrombosis
- 560 **Psychiatric:** Manic reaction, psychosis
- 561 **Renal:** Acute renal failure
- 562 **Resistance mechanism disorders:** Sepsis
- 563 **Respiratory:** Apnea, pleural effusion, pulmonary edema, pulmonary fibrosis, pulmonary infarction,
564 pulmonary hemorrhage, respiratory insufficiency
- 565 **Skin:** Basal cell carcinoma, malignant melanoma
- 566 **Urinary system:** Pyelonephritis, renal calculus
- 567 **Vision:** Retinal detachment

568 **Postmarketing Experience**

569 The following reactions have been identified during postmarketing use of BEXTRA. These reactions
570 have been chosen for inclusion either due to their seriousness, reporting frequency, possible causal
571 relationship to BEXTRA, or a combination of these factors. Because these reactions were reported

572 voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or
573 establish a causal relationship to drug exposure.

574 **General:** Hypersensitivity reactions (including anaphylactic reactions and angioedema)

575 **Skin and appendages:** Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic
576 epidermal necrolysis

577 **OVERDOSAGE**

578 Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea,
579 vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal
580 bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but
581 are rare.

582 Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur
583 following an overdose.

584 Patients should be managed by symptomatic and supportive care following an NSAID overdose.
585 There are no specific antidotes. Hemodialysis removed only about 2% of administered valdecoxib from
586 the systemic circulation of 8 patients with end-stage renal disease and, based on its degree of plasma
587 protein binding (>98%), dialysis is unlikely to be useful in overdose. Forced diuresis, alkalinization of
588 urine, or hemoperfusion also may not be useful due to high protein binding.

589 **DOSAGE AND ADMINISTRATION**

590 **Osteoarthritis and Adult Rheumatoid Arthritis**

591 The recommended dose of BEXTRA Tablets for the relief of the signs and symptoms of arthritis is 10
592 mg once daily.

593 **Primary Dysmenorrhea**

594 The recommended dose of BEXTRA Tablets for treatment of primary dysmenorrhea is 20 mg twice
595 daily, as needed.

596 **HOW SUPPLIED**

597 BEXTRA Tablets 10 mg are white, film-coated, and capsule-shaped, debossed "10" on one side with a
598 four pointed star shape on the other, supplied as:

599 NDC Number	Size
600 0025-1975-31	Bottle of 100
601 0025-1975-51	Bottle of 500
602 0025-1975-34	Carton of 100 unit dose

603 BEXTRA Tablets 20 mg are white, film-coated, and capsule-shaped, debossed "20" on one side with a
604 four pointed star shape on the other, supplied as:

605 NDC Number	Size
606 0025-1980-31	Bottle of 100

607 0025-1980-51 Bottle of 500
608 0025-1980-34 Carton of 100 unit dose
609 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room
610 Temperature].
611 Rx only
612 Revised: Month Year
613 Manufactured for:
614 G.D. Searle LLC
615 A subsidiary of Pharmacia Corporation
616 Chicago, IL 60680, USA
617 Pfizer Inc
618 New York, NY 10017, USA
619 by: Searle Ltd.
620 Caguas, PR 00725

621 818 763 002

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