

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S CONSULT REVIEW

Consultation to HFD-550, Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

NDA: 21-341

Sponsor: G.D. Searle & Co.
Skokie, IL

Date Submitted: January 16, 2001

Drug: Valdecoxib

Pharmacological Category: Nonsteroidal anti-inflammatory drug; cyclooxygenase 2 inhibitor

Formulation: Oral tablets, contain 10, 20 or 40 mg of valdecoxib

Material Reviewed: Integrated summary of safety; final reports for upper G.I. safety studies 017, 044, 045, 047, 048, 053 and umbrella analyses of upper GI events in arthritis trials (study 803); integrated summary of safety, sponsor's proposed US labeling for valdecoxib; integrated summary of risks and benefits; published literature relevant to Valdecoxib; Study 035, NDA 21-341

Reviewer: Mark Avigan, M.D., C.M.

BACKGROUND INFORMATION

A consultation has been sought from the Division of Gastrointestinal and Coagulation Drug Products to review the upper GI safety studies included in NDA 21-341 and provide recommendations regarding their value for inclusion in the label. The listed GI studies include the individual clinical studies 017, 044, 045, 047, 048, 053 and the prospective umbrella analyses (study 803).

Clinical studies included in NDA 21-341 are listed in Tables 1 and 2.

TABLE 1
Pharmacokinetic Studies

Pharmacokinetic Studies	Study¹	Brief Description
Basic PK Profile	001	Single Oral Dose Safety/Tolerability/PK in Healthy Males
	002	Multiple Dose Safety/Tolerability/PK in Healthy Males
	005	Pilot Dose-Ranging Dental Pain/PK
	014	Post-Surgical Dental Pain/PD.
	035	Post-Surgical High-Dose Dental Pain/PK
	003	
	009	Comparative BE/BA of Tablet vs. Capsule Formulations
	018	Food Effect and Antacid PK
	020	BA of Controlled vs. Immediate Release Tablets
	026	Food Effect and BA of Controlled vs. Immediate Release Tablets
	029	Comparative BA of Two Dose Regimens
	050	Comparative BE/BA of Phase II vs. III Tablets
	056	Comparative BE/BA of Phase III Tablet vs. Commercial Tablet Formulation
	070	Absolute BA Study IV vs. Tablet
077	Dose Proportionality PK Study	
078	BE Study of 20 and 40 mg Valdecoxib Tablets	
Comparative PK of Oral Valdecoxib vs. Parenteral Parecoxib Sodium	93-005	IM/Oral Crossover
	93-006	IV/Oral Crossover
	93-014	IM/IV/Oral
ADME Studies	008	PK of [¹⁴ C]Valdecoxib and Valdecoxib
	93-008	PK of IV [¹⁴ C]Parecoxib Sodium and Valdecoxib
	93-009	PK of IM [¹⁴ C]Parecoxib Sodium and Valdecoxib
Special Populations	012	PK Profile in Elderly vs. Young Subjects
	025	PK in Renally Impaired Subjects
	93-012	PK in Hepatically Impaired Subjects
Drug-Drug Interactions	013	Methotrexate Interaction
	034	Glyburide Interaction
	055	Effect of Fluconazole and Ketoconazole
	057	Lithium Interaction
	069	Dextromethorphan Interaction
	073	Midazolam Interaction (with Valdecoxib)
	074	High Dose Methotrexate Interaction
	075	Warfarin Interaction
	93-038	Propofol Interaction
	93-039	Midazolam Interaction (with Parecoxib Sodium)
	93-040	Alfentanil and Fentanyl Interactions

¹Studies with the prefix 93- were conducted as part of the parecoxib sodium clinical program.

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TABLE 2

Treatment of Osteoarthritis	Study	Brief Description
	015	Pilot Efficacy and Dose-Ranging in OA of the Knee
	031	Long-Term Safety in Patients with OA
	047	Renal and UGI Safety in OA and RA
	048	UGI Safety vs. <i>Ibuprofen</i> and <i>Diclofenac</i> in OA
	049	Efficacy and Safety in Symptomatic OA of the Hip
	053	Efficacy and UGI Safety in Symptomatic OA of the Knee
	076	Long-Term Safety Study in Patients with OA or RA
Treatment of Rheumatoid Arthritis	Study	Brief Description
	016	Pilot Efficacy and Dose Ranging in Active RA
	047	Renal and UGI Safety in OA and RA
	060	RA (Flare) Efficacy and Safety
	061	RA (Flare) Efficacy and Safety
	067 [†]	Long-Term Safety Study in Patients with RA
	076 [‡]	Long-Term Safety Study in Patients with OA or RA
GI Differentiation	Study	Brief Description
	017	UGI Safety in Healthy Young Subjects
	044	High-Dose UGI Safety in Healthy Young Subjects
	045	High-Dose UGI Safety in Elderly Subjects
	047	Renal and UGI Safety in OA and RA
	048	UGI Safety vs. <i>Ibuprofen</i> and <i>Diclofenac</i> in OA
	053	Efficacy and UGI Safety in Symptomatic OA of the Knee
	803	Prospective Analysis for Ulcer Complications and GI-Related Adverse Events in Valdecoxib Arthritis Trials
Platelet Differentiation	Study[†]	Brief Description
	021	Platelet/Renal Effects in Healthy Young Subjects
	023	Platelet/Renal Effects in Healthy Elderly Subjects
	042	High-Dose Platelet and Renal Effects in Healthy Elderly Subjects
	043	High-Dose Platelet and Renal Effects in Healthy Subjects
	93-031	Effect of <i>Parecoxib Sodium</i> and <i>Aspirin</i> on Platelet Function
Renal Differentiation	Study	Brief Description
	021	Platelet/Renal Effects in Healthy Young Subjects
	022	Renal Function in Salt-Depleted Healthy Subjects
	023	Platelet/Renal Effects in Healthy Elderly Subjects
	025	PK in Renally Impaired Subjects
	042	High-Dose Platelet and Renal Effects in Healthy Elderly Subjects
	043	High-Dose Platelet and Renal Effects in Healthy Subjects
	047	Renal and UGI Safety in OA/RA vs. <i>Naproxen</i>
	804	Prospective Analysis of Clinically Relevant Renal Events in Valdecoxib Arthritis Trials

[†]Studies with the prefix 93- were conducted as part of the *parecoxib sodium* clinical development program.

[‡]Ongoing study; database frozen for NDA.

The categories of 73 clinical studies to test the efficacy and safety of *valdecoxib* in 17,498 patients (14,332 unique individuals) contained in this NDA are as follows:

- Clinical Pharmacology/Phase I studies
- Arthritis studies
- Analgesic studies including general and oral surgery, primary dysmenorrhea and CABG surgery studies
- Differentiation from NSAIDs



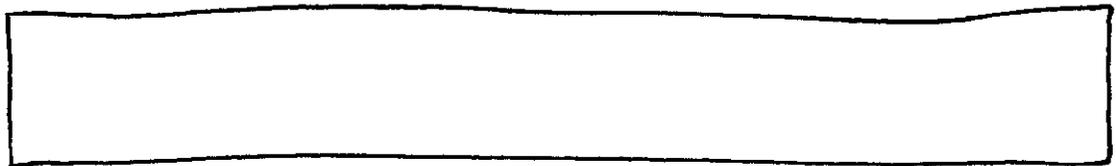
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These studies form an information base which is being analyzed for overall clinical efficacy and safety by Dr. Kent Johnson, Medical Officer, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550).

Valdecoxib is a pharmacologically active cyclooxygenase 2 inhibitor with both anti-inflammatory and analgesic properties.

Proposed Labeling

In the proposed labeling for valdecoxib the following stipulations are made:



- The recommended dose for primary dysmenorrhea is 40 mg QD. ~~_____~~
- The recommended dose for the relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis is 10 mg QD. _____

3



- There are no recommended limitations regarding the duration of treatment.

As will be seen below in a trial in which patients undergoing coronary artery by-pass graph (CABG) were treated sequentially with the I.V. formulation followed by the oral formulation

cases of serious gastrointestinal toxicity occurred during the oral formulation treatment phase.

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SPECIAL GASTROINTESTINAL STUDIES

In the special studies section the following statements and figures are included:

Special Studies

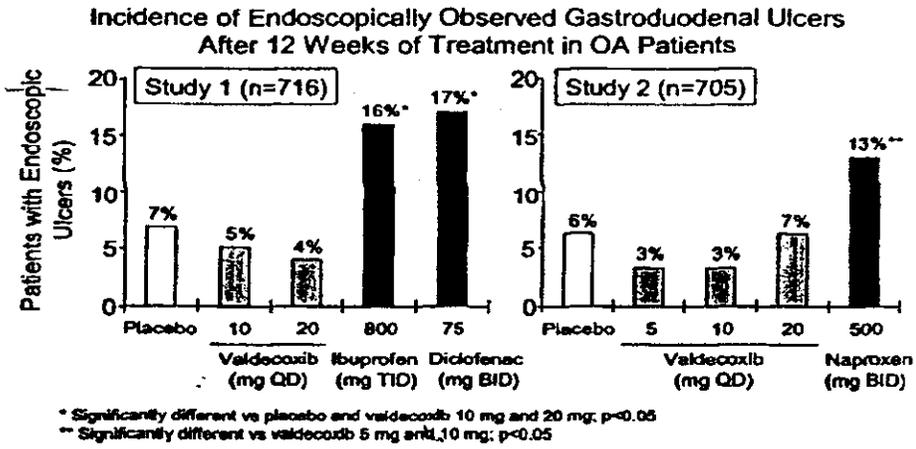
Gastrointestinal:

Scheduled upper GI endoscopic evaluations were performed with Valdecoxib in doses ranging from 5 to 80 mg daily in over 3,200 arthritis patients who were enrolled in three randomized 12-14 week trials using active comparators, two of which included, in addition, placebo controls. In all three studies, Valdecoxib was associated with a statistically significant lower incidence of endoscopic gastroduodenal ulcers over the study period. In the two placebo-controlled studies, the incidence of endoscopic gastroduodenal ulcers with valdecoxib 5 to 20 mg daily was similar to that observed in placebo-treated patients. Figure 1 summarizes the incidence of gastroduodenal ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no gastroduodenal ulcers.

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Figure 1

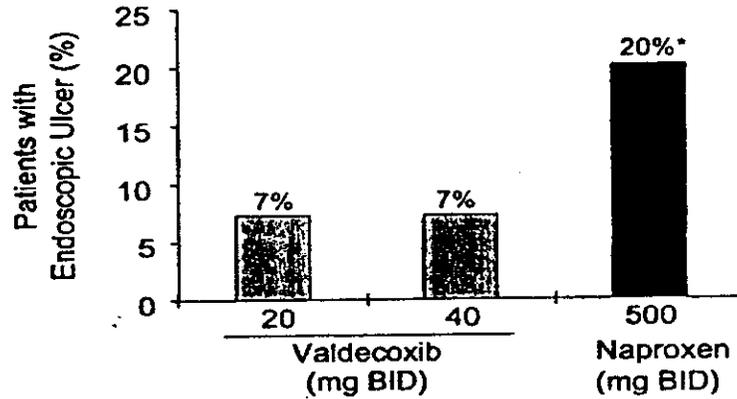


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Figure 2

Incidence of Endoscopically Observed Gastroduodenal Ulcers
After 14 Weeks of Treatment in RA Patients (n=405)



* Significantly different vs. both valdecoxib treatments $p < 0.05$

Figure 2 summarizes the incidence of gastroduodenal ulcers at week 14 in RA patients in whom baseline endoscopies revealed no gastroduodenal ulcers.

Use with Aspirin:

Approximately 13% of patients (440/3,389) enrolled in the three endoscopic studies were taking aspirin (≤ 325 mg daily). In the valdecoxib groups, the endoscopic ulcer rate after 12-14 weeks of treatment was higher in aspirin users than in nonusers. However, at recommended doses of valdecoxib the incidence of ulcers in these aspirin users was known than that observed in the NSAID active comparator groups, with or without aspirin.

In the Warning Section from the proposed labeling of valdecoxib the following statements are included:

WARNINGS

Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation:

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach or intestine has been observed in patients treated with valdecoxib, albeit infrequently. Physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms.

Among 3,038 patients who received valdecoxib in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 10 to 80 mg, 5 (0.165) experienced significant upper GI bleeding, occurring 15 to 117 days after initiation of dosing. In the absence of low dose aspirin the rate was 0.09% (2/2,267). Approximately 27% of these 3,038 patients were in studies that required them to be free of ulcers by endoscopy at study entry (see CLINICAL STUDIES – Special Studies – Gastrointestinal). Thus it is unclear if this study population is representative of the general population. Prospective, long-term studies to compare

TABLE 3

Protocol No. Report No. Short Title	No. of Investigators Country Start Date	Population	Study Design (Duration of Treatment)	Treatment Regimen (N/group)
Gastrointestinal Differentiation Studies				
P: N91-97-02-017 R: N91-99-06-017 UGI Safety in Healthy Subjects	Two Investigators United States 12 October 1997	Healthy adult males and females	Randomized, Double-Blind, Placebo- Controlled, Parallel Group, Multicenter (6.5 days)	Valdecoxib 10 mg BID (N=47), 25 mg BID (N=45); or naproxen 500 mg BID (N=46); or placebo (N=46)
P: N91-98-02-044 R: N91-99-06-044 High-Dose UGI Safety in Healthy Subjects	One Investigator United States 26 September 1998	Healthy adults	Randomized, Double-Blind, Placebo- Controlled, Parallel Group, Single Center (6.5 days)	Valdecoxib 40 mg BID (N=63); or naproxen 500 mg BID (N=62); or placebo (N=63)
P: N91-98-02-045 R: N91-00-06-045 High-Dose UGI Safety in Elderly Subjects	Four Investigators at Four Sites United States 27 October 1998	Normal healthy elderly subjects	Randomized, Double-Blind, Placebo- Controlled, Parallel Group, Multicenter (6.5 days)	Valdecoxib 40 mg BID (N=62); or naproxen 500 mg BID (N=62); or placebo (N=62)
P: N91-99-02-047 R: N91-00-06-047 Renal Safety and Gastroduodenal Ulcer vs. Naproxen in OA or RA	148 Investigators at 148 Sites North America 25 August 1999	Adult males or females diagnosed with OA or RA	Randomized, Double-Blind, Active-Controlled, Multicenter, Parallel Group (26 weeks)	Valdecoxib 20 mg BID (N=399), or 40 mg BID (N=404), or naproxen 500 mg BID (N=415)
P: N91-98-02-048 R: N91-00-26-048 Incidence of UGI Ulcer Valdecoxib vs. Ibuprofen and Diclofenac Sodium in OA	Eighty-one Investigators North America 14 April 1999	Adult males or females diagnosed with osteoarthritis of the knee, aged 25-88 years, inclusive	Randomized, Double-Blind, Placebo- Controlled, Parallel Group, Multicenter (12 weeks)	Valdecoxib 10 mg QD (N=204), 20 mg QD (N=219); or ibuprofen 800 mg TID (N=207); or diclofenac 75 mg BID (N=212); or placebo (N=209)
P: N91-99-02-053 R: N91-00-06-053 Efficacy and UGI Safety in OA of the Hip	88 Investigators at 88 Sites United States 4 May 1999	Patients with symptomatic OA of the knee	Randomized, Double-Blind, Placebo- and Active-Controlled, Multicenter, Parallel Group (12 weeks)	Valdecoxib 5 mg QD (N=201), 10 mg QD (N=206), 20 mg QD (N=202), or naproxen 500 mg BID (N=205), or placebo (N=205)

INTRODUCTION

The previously approved COX-2 selective NSAIDs celecoxib and rofecoxib have been linked to a reduced incidence of endoscopic ulcers when compared to non-selective NSAIDs. Based on studies that were performed at the time of the original NDA submissions, the labeling of both products emphasizes statistically significant reduction in gastroduodenal ulcers based on scheduled upper G.I. endoscopic evaluations performed in OA and RA patients in 6, 12 and 24-week trials. Active comparators have included diclofenac 75 mg BID, ibuprofen 800 mg TID and naproxen 500 mg BID in the case of celebrex trials¹ and ibuprofen in the case of rofecoxib trials (recommended doses of active comparators for OA/RA).² Although the cumulative incidence of gastroduodenal ulcers based on serial endoscopies has been reproducibly lower in study patients treated with COX-2 inhibitors compared to nonselective NSAIDs, at the time of the original labeling of celecoxib and rofecoxib, the relationship of endoscopic ulcer rates to the risk of developing complicated GI ulcers (bleeding, perforation or obstruction) and/or symptomatic GI ulcers was not defined. This prompted the celecoxib long-term arthritis safety study (CLASS study) in which the primary endpoint was the incidence of complicated ulcers in celebrex treated compared to ibuprofen and diclofenac-treated subjects. 7,982 subjects (72% with osteoarthritis, 28% with rheumatoid arthritis) were entered into the CLASS study without being stratified according to use of low dose aspirin (approximately 21% of subjects), comorbid conditions that may increase the risk for GI bleeding (e.g. treatment with oral corticosteroids, or anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status). Although the celecoxib group (n=3,995) trended towards a reduction of complicated upper GI events compared to other NSAID users, the rate did not achieve statistical significance compared to nonselective NSAIDs (0.8% vs 1.4%; p=0.09). Although the incidence of symptomatic ulcers and ulcer complications as a composite was lower in celecoxib 400 mg BID users than in those treated with ibuprofen 800 mg TID, there was no difference between the celecoxib treated patients and those treated with diclofenac 75 mg BID.

The simultaneous use of aspirin may significantly alter the toxicity profile of COX-2 inhibitors. When patients were analyzed according to use/nonuse of low dose aspirin the following results emerged:

Aspirin non-users:

- Improvement of complicated ulcer rates in the celecoxib treatment group depended on the active comparator that was used. When compared to diclofenac no difference in side effect

¹ FE Silverstein et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study*. JAMA 2000 Sep 13;284(10):1247-55

LS Simon et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. *Arthritis Rheum* 1998 Sep;41(9):1591-602

² C. Bombardier et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000 Nov 23; 343(21):1520-8,

L. Laine et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group. *Gastroenterology* 1999 Oct; 117(4):776-83

incidence was observed. In contrast, celecoxib was associated with a reduction in complicated ulcers when compared to ibuprofen. When using the composite of complicated and symptomatic ulcers as the parameter of evaluation the result was also active comparator dependent.

Aspirin users:

- Low dose aspirin practically eliminated the relative reduction of complicated ulcer incidence in celebrex users when compared to subjects treated with non-selective NSAIDs (1.6% Kaplan-Meier cumulative rate vs 0.4% in non-aspirin users). In the case of concomitant ibuprofen and aspirin usage background complicated ulcer rates were not increased over ibuprofen alone and in fact there was a statistically not significant paradoxical reduction (0.4% vs 0.8%).
- Likewise, concomitant low dose aspirin usage was associated with an increase in the symptomatic ulcer cumulative rate of celecoxib users (4.9% vs 1.1%). In contrast low dose aspirin usage did not affect the symptomatic ulcer rate of ibuprofen users (3.0% vs 3.3%).

A limitation of the interpretation of these aspirin effects on complicated/symptomatic ulcer incidence in study subjects treated with celecoxib, is the absence of an "aspirin-alone" treatment arm. For this reason the individual contribution of the COX-2 inhibitor to side effect incidence cannot be precisely calculated. It is possible that when administered together these agents cause more mucosal toxicity than either agent when administered alone.

Based on this information treatment with celecoxib does not appear to confer an advantage for the development of clinically significant GDUS in individuals who are simultaneously medicated with aspirin. The widespread use of aspirin in the aging population as a prophylaxis against cardiovascular disease makes it more important to formulate a comparative analysis of hazards associated with the use of COX-2 vs COX-1 inhibitors.

The clinical relevance of ulcers identified during endoscopy at scheduled intervals remains uncertain. Clear differences in the endoscopic rates of gastroduodenal ulcers between subjects treated with celebrex and those treated with non-selective NSAIDs are not necessarily mimicked by the corresponding rates of complicated and symptomatic ulcers. When the cumulative rates of complicated ulcers associated with celecoxib usage are compared to those associated with ibuprofen, the absolute risk reduction identified in the CLASS study was 0.4%. Absolute risk reduction can be converted to the number of patients that need to be treated to prevent one additional bad outcome over a given period of time. The measure is based on the following equation:

$$\text{Number Needed to Treat (NNT)} = 1/\text{Absolute Risk Reduction (ARR)}$$

Based on differences in risk for complicated ulcers in the celecoxib and ibuprofen treatment groups, a difference in outcomes will only be detected in one of 250 treated patients. Similarly, the 1.9% ARR in symptomatic ulcer incidence between celebrex and ibuprofen non-aspirin users translates to a NNT of 52 patients in order to obtain one different outcome. The

observation that diclofenac induces a higher rate of endoscopically detected ulcers than celecoxib, is of doubtful clinical relevance because the rates of complicated and symptomatic ulcers associated with these drugs are virtually the same.

Recently, an approvable letter was issued in response to a supplemental NDA requesting labeling changes of celecoxib based on results of the CLASS study. Outstanding issues that surround current negotiations with the sponsor include

- Need to establish an appropriate emphasis on the hierarchy of importance of the following drug associated upper GI side effect endpoints:
 - Complicated ulcers whether preceded or accompanied by symptoms or not
 - Symptomatic ulcers
 - Endoscopic ulcers

To be informative, the labeling must conceptually link these endpoints. Moreover, it is imperative that the clinically most significant measures of celebrex associated side effects are not overshadowed by surrogate endoscopic measures. This need will be met by consideration of

- The order of presentation of the endpoints.
- The text content and numbers of figures/tables dedicated to each endpoint.

Because endoscopic ulcers are necessary precursor lesions of complicated and symptomatic ulcers, they have been presumed to be a valid surrogate marker for the risk to develop the clinically relevant adverse events. The following concerns have been raised about the validity of this surrogacy:

- Previous endoscopic studies have not been designed to comprehensively analyze patients according to risk for ulcer complications such as bleeding, obstruction or perforation. As alluded to above the characteristics that lend themselves to such a high risk include a prior history of peptic ulcer disease and/or gastrointestinal bleeding, treatment with oral corticosteroids, treatment with anticoagulants, long duration of NSAID therapy, smoking, alcoholism, older age and general health status. Despite the observation that in the total pool of study subjects the endoscopic ulcer rate has been lower in celebrex users compared to users of nonselective NSAIDs, differences of the complication rates may not be significant in individuals at high risk. This question will require further study.
- As alluded to above, information concerning the concomitant use of low dose aspirin, a nonselective COX-1 inhibitor, appears to eliminate the advantage linked to ulcer incidence conferred by the Cox-2 inhibitor. It is not inconceivable that toxic effects conferred by COX-2 inhibitors on the GI mucosa associated with cyclooxygenase inhibitors may be additive and/or synergistic when members of both classes are administered simultaneously. This possibility has been raised by experimental results in a rat model in which the simultaneous administration of both a selective COX-2 and COX-1 inhibitor has been observed to induce significant gastric injury not observed when either inhibitor was

administered alone³. The possibility of synergistic toxicity will require further study because many of the patients for whom COX-2 inhibitors are being targeted require concomitant treatment with low dose aspirin for the prophylaxis of myocardial infarction and other cardiovascular diseases. The importance of prospective studies addressing this question cannot be overemphasized.

GI Safety Studies Presented In NDA 21-341

Six studies comprised of regularly scheduled endoscopies were performed to measure the upper GI effects of valdecoxib (studies 017, 044, 045, 047, 048 and 053; see Table 8.a). These included three studies of short-term treatment (6.5 days) in normal subjects (studies 017, 044 and 045), and three studies of 26 week or 12 week treatment in patients with OA or RA (studies 047, 048 and 053; see Table 8.a). The primary endpoint in each trial was gastroduodenal ulcer incidence at the end of the dosing period.

Short-term Upper GI Endoscopy Studies in Healthy Subjects

Studies 017, 044 and 045 were randomized, double-blind studies that enrolled healthy volunteers who underwent upper GI endoscopy immediately before and again after receiving study medication. Study enrollees were shown to be without petechiae, erosions or ulcers at baseline endoscopy. In addition to ulcer enumeration, measurement of mucosal injury using an endoscopy scoring scale for gastric and duodenal mucosa was performed (see Table 4).

Table 4
Endoscopy Scoring Scale for Gastric and Duodenal Mucosae

Score	Description
0	No visible lesions
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions*
5	11-25 erosions*
6	>25 erosions*
7	Ulcer**

* An erosion was defined as any break in the mucosa without depth.

** An ulcer was defined as any lesion of any size with unequivocal depth for Studies 017, 044, and 045. In Studies 048, 053 and 047, an ulcer was defined as any break in this mucosa at least 3 mm in diameter with unequivocal depth.

³ Wallace, JL, McKnight, W, Reuter, BK, and Vergnolle, N., NSAID-Induced Gastric Damage in Rats: Requirement for Inhibition of Both Cyclooxygenase 1 and 2; Gastroenterology 2000; 119: 706-714.

In these three short-term endoscopy studies 554 healthy subjects received study medication and 549 underwent post-treatment endoscopies. Each study contained a valdecoxib treatment arm (Studies 044 and 045 - 40 mg BID; Study 017 - 10 mg BID and 25 mg BID), in conjunction with a placebo treatment arm and an active non-selective NSAID (naproxen 500 mg BID). The ulcer incidence rates measured in these studies are shown in Table 5

TABLE 5
Ulcer Incidence Rates in Studies 017, 044 and 045

Treatment	Placebo	Valdecoxib		Naproxen 500 mg BID	
		10 mg BID	25 mg BID		40 mg BID
Gastroduodenal					
Study 017	0% (0/46)	0% (0/47)	0% (0/44)	--	9% (4/44)*
Study 044	0% (0/62)	--	--	2% (1/63)	6% (4/62)
Study 045	3% (2/61)	--	--	0% (0/60)	18% (11/60)*
Total	1% (2/169)	0% (0/47)	0% (0/44)	1% (1/123)	11% (19/166)
Gastric					
Study 017	0% (0/46)	0% (0/47)	0% (0/44)	--	9% (4/44)*
Study 044	0% (0/62)	--	--	2% (1/63)	6% (4/62)
Study 045	3% (2/61)	--	--	0% (0/60)	17% (10/60)*
Total	1% (2/169)	0% (0/47)	0% (0/44)	1% (1/123)	11% (19/166)
Duodenal					
Study 017	0% (0/46)	0% (0/47)	0% (0/44)	--	2% (1/44)
Study 044	0% (0/62)	--	--	0% (0/63)	0% (0/62)
Study 045	0% (0/61)	--	--	0% (0/60)	3% (2/60)
Total	0% (0/169)	0% (0/47)	0% (0/44)	0% (0/123)	2% (3/166)

Derived from individual Final Study Reports, except for Total. (No statistical analyses done for Total.)

Cells show % of subjects and (number of subjects with ulcer/number in treatment group). A subject was counted as having a gastroduodenal ulcer if either a gastric or duodenal ulcer (or both) was present. Only subjects who had Posttreatment endoscopy are shown.

* Significantly different from placebo and all valdecoxib treatments; $p < 0.05$.

Not surprisingly as has been demonstrated for other COX-2 inhibitors including celecoxib and rofecoxib gastroduodenal ulcer incidences in treatment groups receiving naproxen, the non-selective NSAID comparator, were in a greater statistically significant fashion than the incidences in either the placebo or valdecoxib treatment groups (studies 017 – 9% in the naproxen treatment arm vs 0% the placebo treatment and low-dose valdecoxib treatment (10 mg BID and 25 mg BID) groups; study 045 – 18% in the naproxen treatment arm vs 3% in the placebo treatment group and 0% in the valdecoxib (40 mg BID) treatment group. Although a statistically significant difference between the nonselective NSAID active comparator and the valdecoxib treatment groups was not achieved in study 044 (gastroduodenal ulcer rate in the naproxen treatment arm was 6% vs 2% in the valdecoxib 40 mg BID treatment group), this study was associated with an unexpectedly low gastroduodenal ulcer rate in the naproxen treatment arm. Not surprisingly, most of the ulcers observed in the studies were gastric ulcers and these findings were reflected by statistical differences in gastric ulcer rates but not duodenal ulcer rates (the power to detect differences in the occurrence of duodenal ulcers was low). None of the ulcers observed in these studies were symptomatic and as such none were reported as adverse events. When non-ulcer erosions were scored as lesions in conjunction with ulcers, statistical differences between the incidence rates of composite lesions (erosions and/or ulcers) were observed between the naproxen and all of the valdecoxib treatment arms ($p < 0.05$) in all of the three studies. This result is consistent with previous findings of upper GI endoscopic studies of other COX-2 inhibitors. It should be noted that almost invariably the erosions/ulcers noted in

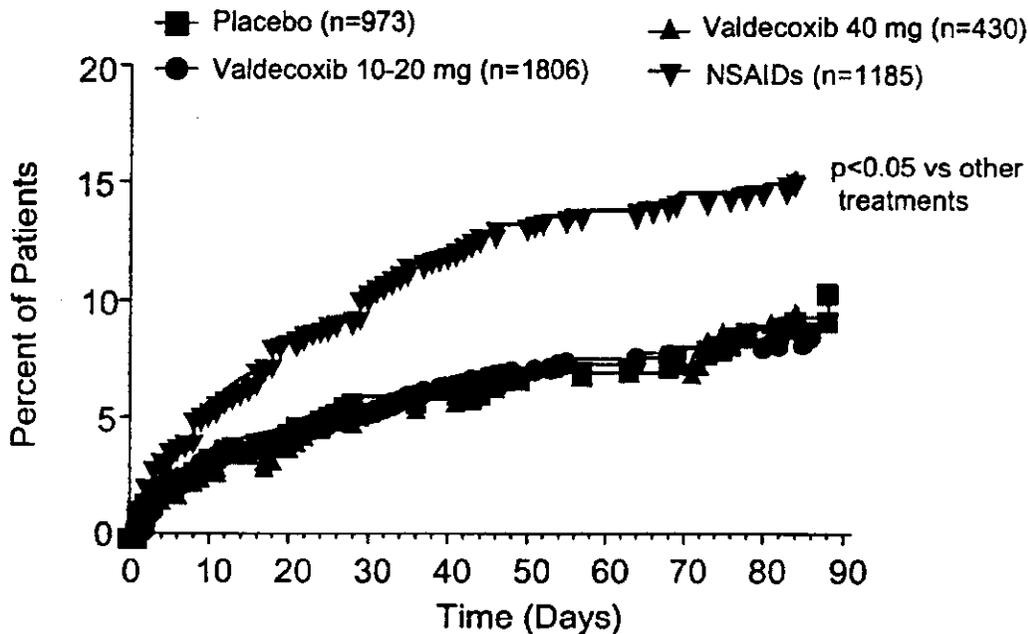
such short-term drug exposure studies are evanescent and not linked to clinical sequelae. Consequently, results from these bioassays are of uncertain clinical relevance.

Upper GI Endoscopy Studies in Arthritis Patients

Three randomized, double-blind endoscopy studies (studies 048, 053 and 047) were performed in patients with OA or RA treated with valdecoxib or a non-selective NSAID (see Table 3). Study 048 and 053 were 12 week trials which included a placebo group whereas study 047 was a 26 week active control study only. In the placebo controlled studies each of the valdecoxib treatment arms as well as the non-selective NSAID and placebo treatment arms consisted of approximately 200 patients that originated from more than 80 study sites. Subjects were excluded from the studies if they had greater than 10 gastric/duodenal erosions or gastroduodenal ulcers at pre-treatment endoscopy. The 200 patient per treatment group sample size was calculated to be sufficient to detect differences between gastroduodenal ulcer rates of 5% in the valdecoxib treatment group and 16% or larger in the comparative NSAID groups with a power of 80% and a 0.017 level of significance. In study 048 the active comparator non-selective NSAID treatment arms were ibuprofen 800 mg TID and diclofenac 75 mg BID, whereas in Studies 047 and 053 the active comparator was naproxen 500 mg BID. Confounding risk factors for gastroduodenal ulceration in subjects enrolled in studies 048 and 053 are shown in Table 14.g. In the 10 mg of the valdecoxib treatment arm of Study 048 there were only nine low dose ASA users whereas in the other active treatment arms the numbers of low dose ASA users ranged between 16 and 18. Similarly, in study 053 in the 5 mg valdecoxib treatment arm only 37 patients manifested *H. pylori* positive serology whereas in the non-selective NSAID treatment arm 43 patients were serologically positive. In addition, in the 5 mg valdecoxib treatment arm, 10 patients had a history of GDU whereas in the non-selective NSAID treatment arm 15 patients had a history of ulcers. Although these differences are modest they have the potential of impacting on small differences in the rates of ulcer complications linked to these studies. Figure 1 shows the GDU rates in the valdecoxib and non-selective NSAID treatment arms in studies 048 and 053. Although in both studies statistical differences were noted in ulcer rates between the non-selective NSAID treatment arms and the 10 mg valdecoxib treatment arm in study 053 a statistical difference between the naproxen treatment arm and the valdecoxib 20 mg treatment arm was not achieved. (Nonetheless, the non-selective NSAID was associated with a higher incidence of gastroduodenal ulcers; see Figure 3).

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Figure 3



• moderate to severe abdominal pain, dyspepsia, nausea

As in the case of the short-term bioassays the duodenal ulcer rates were small compared to the gastric ulcer rates in all the patient studies. It should be emphasized that in studies 048 and 053 the highest dose of valdecoxib that was tested was 20 mg which is the currently recommended dose for treatment of osteoarthritis and adult rheumatoid arthritis in the proposed draft labeling. However, a higher dose of 40 mg is recommended for other conditions including management of acute pain, pre-operative dosing and primary dysmenorrhea. This higher dose was used in one of the treatment arms of study 047 which was a randomized, double-blind, parallel group, multi-center 26 week study of valdecoxib 20 and 40 mg BID treatment arms with an active non-selective NSAID comparator (naproxen 500 mg BID). All patients had a pre-treatment endoscopy and a follow-up endoscopy at week 14 of treatment. Approximately 400 patients were randomized into each treatment arm. The incidences of confounding risk factors for the development of gastroduodenal ulceration for patients enrolled in study 047 are shown in Table 6.

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TABLE 6

Demographics, Medical History, Baseline *H. pylori* Status, and Aspirin Use: Study 047

	Valdecoxib 20 mg BID (N=399)	Valdecoxib 40 mg BID (N=404)	Naproxen 500 mg BID (N=415)
Mean Age (yrs)	56.2	56.1	55.8
Female	72	72	71
RA patients	49	51	51
Age ≥ 65 years	27	29	23
Age > 75 years	7	7	4
History of GI Bleeding	2	2	2
History of Gastroduodenal Ulcer	11	10	11
History of Cardiovascular Disease	45	46	45
<i>H. Pylori</i> Positive Serology	25	26	32
Aspirin Use (≤325 mg/day)	14	11	14

Entries are % of patients except mean age
Derived from individual Final Study Report

It is apparent that the naproxen 500 mg BID treatment arm contained a slightly higher number of patients who were serologically positive for *H. pylori* compared to the valdecoxib treatment arms (32 vs 25 and 26). Nonetheless, the baseline risks for complicated GDUs appear to be well balanced between all treatment arms. In study 047 over the 14 week treatment period the incidence of GDUs were statistically significantly lower in valdecoxib treated patients for both doses of valdecoxib (20 mg and 40 mg BID) compared to patients receiving naproxen (see Table 7).

TABLE 7

Ulcer Incidence Rates: High-Dose OA and RA Safety Trial

	Valdecoxib 20 mg BID (N=399)	Valdecoxib 40 mg BID (N=404)	Naproxen 500 mg BID (N=415)
Gastroduodenal			
All Patients	6% (14/253)	9% (24/259)	23% (63/272)*
RA Patients	7% (9/127)	7% (10/135)	20% (29/143)*
OA Patients	4% (5/126)	11% (14/124)**	26% (34/129)*
Gastric			
All Patients	4% (9/249)	8% (20/258)	18% (49/265)*
RA Patients	4% (5/124)	6% (8/135)	18% (25/140)*
OA Patients	3% (4/125)	10% (12/123)**	19% (24/125)*
Duodenal			
All Patients	2% (6/252)	2% (5/257)	7% (19/267)*
RA Patients	3% (4/126)	1% (2/134)	4% (6/139)*
OA Patients	2% (2/126)	2% (3/123)	10% (13/128)*

* Significantly different from both valdecoxib treatments; p<0.05.

** Significantly different from valdecoxib 20 mg BID; p<0.05

Entries are % of patients with ulcer (No. with ulcer/ No. with known result). Known endoscopy results include an ulcer detected at any time, or a finding of no ulcer at an endoscopy performed at 98 ± 7 days. Derived from individual Final Study Report.

It should be noted that significantly higher incidences of GDUs were observed with valdecoxib 40 mg BID in osteoarthritis patients when compared to 20 mg BID. Therefore, it appears that although valdecoxib at both 20 mg BID and 40 mg BID doses were associated with lower ulcer incidence rates compared to naproxen there was a dose related effect on ulcer incidence associated with the COX-2 inhibitor. Once again, differences in duodenal ulcer rates between the non-selective NSAID comparator and each of the valdecoxib treatment arms were comparatively small (7% vs 2% for all patients entered in the study). Moreover, no differences in duodenal ulcer incidence was noted between each of the valdecoxib treatment arms.

In study 047 (see Table 8), both low dose ASA use and elderly age (≥ 65 years) were linked to higher GDU rates in valdecoxib users (both 20 mg BID and 40 mg BID doses). In addition, a history of GDUs was associated with increased risk for GDUs in the valdecoxib 40 mg treatment arm.

TABLE 8

**Effect of Demographic Covariates and Potential Risk
Factors on Gastrointestinal Ulcer Incidence Rates:
Study 047**

	Valdecoxib 20 mg BID	Valdecoxib 40 mg BID	Naproxen 500 mg BID
Low dose Aspirin (<325 mg/day) Use			
Users	12% (6/49)	26% (10/38)*	13% (7/54)
Nonusers	3% (9/296)	5% (17/317)	19% (59/310)
Age			
≥ 65 years	8% (8/99)*	14% (15/107)*	27% (24/88)*
< 65 years	3% (7/246)	5% (23/248)	15% (42/276)
H. pylori status (CLOtest)			
Positive	7% (4/61)	10% (7/71)	25% (19/76)
Negative	4% (10/230)	9% (19/215)	19% (43/232)
History of Gastroduodenal Ulcer			
History	8% (3/36)	28% (10/36)*	37% (16/43)*
No History	4% (12/309)	5% (17/319)	16% (50/321)
* Significant within treatment difference; $p < 0.05$.			
Enteries are % of patients with ulcer (No. with ulcer/No. with posttreatment endoscopy) at first visit.			
Derived from individual Final Study Report			

These results point to an interplay between other risk factors and the potential to develop GDUs in specialized patients being treated with valdecoxib. The results underline the need for adequately powered studies to measure the risk to develop GDUs associated with valdecoxib use for 3 months or longer in each of the aforementioned subsets of the population.

Clinically Significant Upper GI Events in Arthritis Studies

Clinically significant upper GI events of pooled data across multiple valdecoxib arthritis studies were analyzed (Study 803). The pooled analysis incorporated studies in which the comparator nonselective NSAID treatment arms consisted of naproxen 500 mg BID, diclofenac 75 mg BID

or ibuprofen 800 mg TID. The clinically significant upper GI events that were scored were a composite endpoint comprised of bleeding, perforation or gastric outlet obstruction events. The analysis encompassed data from 6 controlled valdecoxib arthritis studies (studies 047, 048, 049, 053, 060 and 061) and three long-term open label trials (studies 031, 067 and 076). The durations of exposure to valdecoxib in these studies ranged between 12 weeks and one year. Asymptomatic ulcers identified during scheduled endoscopies by investigators were not scored as significant events for the purpose of this analysis. Members of a full Gastrointestinal Events Committee who were blinded to both studies as well as treatment assignment adjudicated each case submitted to the sponsor by consensus in order to determine, by prespecified criteria, whether a clinically significant upper GI event had occurred. The criteria for each category of significant upper GI events were:

1. Upper GI bleeding associated with a gastric or duodenal ulcer or large erosion proven by endoscopy or upper GI barium X-ray linked to one of the following 7 clinical presentations:
 - Hematemesis
 - Active bleeding or stigmata of a recent hemorrhage identified endoscopically
 - Melena
 - Hemoccult positive stools and a fall in hematocrit of $\geq 5\%$ points or a reduction of globulin ≥ 1.15 g/dL.
 - Hemoccult positive stools with orthostasis
 - Hemoccult positive stools associated with blood transfusions of 2 or more units
 - Hemoccult positive stools associated with blood in the stomach determined by nasogastric aspiration or endoscopy
2. Upper GI perforation evidenced by unequivocal findings/signs
3. Gastric outlet obstruction based on endoscopic and/or upper GI barium X-ray evidence.

An analysis of the composite of the upper GI events in study 803 was performed by calculation of crude and Kaplan-Meier rates of events of occurrence by time interval and comparisons between treatment groups were analyzed by log-rank test. A similar analysis of clinically significant upper GI events combined with symptomatic ulcers was performed. Symptomatic ulcers were defined as gastroduodenal ulcers first were detected after presentation of a gastrointestinal sign or symptom either during unscheduled or scheduled endoscopies. Ulcers were defined as breaks in the mucosa ≥ 3 mm with unequivocal depth documented either by endoscopy or barium X-ray. A separate analysis was performed on the subset of patients concomitantly treated with low dose aspirin (≤ 325 mg/day).

A total of 5,932 patients enrolled in the 12 to 16 week controlled arthritis trials (studies 047, 048, 049, 053, 060 and 061) received at least one dose of medication (NSAID or placebo). The demographic characteristics of patient enrollees are shown in Table 9.

TABLE 9

Patient Demographics, Medical History and Concurrent Medications: 12- to 26-Week Controlled Arthritis Trials

Characteristic	Placebo (n=973)	Valdecoxib 5-80 mg/day (n = 3359)	NSAIDs (n = 1600)
Mean age (range), y	58.8 (19-88)	57.2 (19-90)	59.4 (18-88)
≥65 years of age (%)	35	30	32
≥75 years of age (%)	9	8	9
Women, (%)	71	72	71
Race, (%)			
White	81	80	81
Black	8	9	10
Hispanic	10	9	7
Asian	0	1	1
Other	1	1	1
Primary disease, (%)			
RA	45	51	41
Potential Risk Factor (%)			
History of GI bleeding	1	1	2
History of GI ulcer	10	11	12
Positive <i>Helicobacter pylori</i> serology (%)	16	19	25
Test not performed	57	46	35
Concurrent medications, (%)			
Aspirin (≤325 mg daily)	13	14	15
Corticosteroids	20	24	20

Data derived from Tables T4, T5 and T6, Study 803 final report

From this Table it is apparent that information about *H. pylori* serological status in all patients was not available. As alluded to above positive serology does not necessarily indicate active *H. pylori* infection. Therefore positive serology does not identify with high specificity individuals who may be at increased risk for the development of gastroduodenal ulcers. The analysis of study participants in the valdecoxib treatment arms of the combined studies includes individuals treated with a range of doses of valdecoxib. Some study subjects were treated with doses that are subtherapeutic. In contrast, in the nonselective NSAID treatment arms doses were in the high therapeutic range. Therefore, comparability of safety event outcomes between the COX-2 inhibitor treatment arms and the nonselective NSAID arms is difficult to assess because of the absence of absolute dose equivalence.

The wide rate of clinically significant upper GI events was 0.58% (7 cases/1,197 treated subjects). Although in study 048 the numbers of subjects treated with ibuprofen and diclofenac

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were too small to determine whether these rates were similar to the rate associated with naproxen treatment in the CLASS study it is likely that they are lower and closer to those associated with valdecoxib treatment.

In the composite of controlled arthritis studies in which the non-selective NSAID presentation is heavily weighted in the number of subjects treated with naproxen 500 mg BID compared to ibuprofen 800 mg TID and diclofenac 75 mg BID (n=1,181, n=207 and n=212, respectively; sponsor's Table T1).

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Table T1
Patient Disposition by Study and Treatment

RANDOMIZED CONTROLLED STUDIES	Intent-to-Treat Cohort									
	PLACEBO	VALDECOXIB 5 mg QD	VALDECOXIB 10 mg QD	VALDECOXIB 20 mg QD	VALDECOXIB 20 mg BID	VALDECOXIB 40 mg QD	VALDECOXIB 40 mg BID	NAPROXEN 500 mg BID	IBUPROFEN 800 mg TID	DICLOFENAC 75 mg BID
N91-98-02-048	209		204	219					207	212
N91-99-02-047					399		403			
N91-99-02-049	117	120	111					415		
N91-99-02-053	205	201	205	201				118		
N91-99-02-060	222		209	212		221		204		
N91-99-02-061	220		226	219		209		225		
TOTAL	973	321	955	851	399	430	403	1181	207	212

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Consistent with findings of the CLASS study, a reduction of incidence of clinically significant upper GI events was apparent only in non-ASA users treated with valdecoxib compared to the non-selective NSAID treatment arms. This difference was not apparent in ASA users (0.07% vs 0.5% and 0.6% and 0.0%) see sponsor's Table T12.

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Table T12
Risk Factor Analysis of Clinically Significant UGI Events
Randomized Controlled Studies

	Intent-to-Treat (ITT) Cohort		P-Value (a)	Treatment by Factor Interaction	Factor Effect
	PLACEBO (N = 973)	VALDECOXIB (N = 3359)			
AGE (years)					
<75	0/ 890 (0.0%)	4/3101 (0.1%)	6/1464 (0.4%)	0.796	0.294
≥75	0/ 83 (0.0%)	1/ 258 (0.4%)	1/ 136 (0.7%)		
P-VALUE (b)	0.309	0.529			
GENDER					
MALE	0/ 286 (0.0%)	1/ 950 (0.1%)	3/ 465 (0.6%)	0.421	0.733
FEMALE	0/ 687 (0.0%)	4/2409 (0.2%)	4/1135 (0.4%)		
P-VALUE (b)	0.677	0.427			
DISEASE TYPE					
OA	0/ 531 (0.0%)	4/1662 (0.2%)	4/ 943 (0.4%)	0.203	0.436
RA	0/ 442 (0.0%)	1/1697 (<0.1%)	3/ 657 (0.5%)		
P-VALUE (b)	0.243	0.913			
ASPIRIN USE					
ANY	0/ 126 (0.0%)	3/ 477 (0.6%)	0/ 242 (0.0%)	0.007	0.394
NONE	0/ 847 (0.0%)	2/2882 (<0.1%)	7/1358 (0.5%)		
P-VALUE (b)	0.017	0.993			
HISTORY OF CARDIOVASCULAR DISEASE					
YES	0/ 457 (0.0%)	4/1571 (0.3%)	5/ 780 (0.6%)	0.685	3.048
NO	0/ 516 (0.0%)	1/1788 (<0.1%)	2/ 820 (0.2%)		
P-VALUE (b)	0.159	0.237			
HISTORY OF UPPER GI BLEEDING					
YES	0/ 13 (0.0%)	0/ 42 (0.0%)	1/ 31 (3.2%)	0.361	0.179
NO	0/ 960 (0.0%)	5/3317 (0.2%)	6/1569 (0.4%)		
P-VALUE (b)	0.994	0.043			
HISTORY OF GASTRODODENAL ULCER					
YES	0/ 100 (0.0%)	3/ 352 (0.9%)	2/ 195 (1.0%)	0.233	0.006
NO	0/ 873 (0.0%)	2/1007 (<0.1%)	5/1405 (0.4%)		
P-VALUE (b)	0.005	0.184			

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

In these valdecoxib randomized controlled studies in ASA users there was an unexpected absence of cases of clinically significant upper GI events among non-selective NSAID users, whereas the concomitant use of valdecoxib and aspirin was associated with an incidence of 0.6%. Therefore, the use of aspirin caused an increase in risk for clinically significant upper GI events between 8 and 9 fold only in patients treated with valdecoxib. Importantly, in addition to the use of the low dose ASA, a history of GDU was associated with a 13 to 14 fold increase in risk for the development of clinically significant upper GI events in patients treated with valdecoxib. This increase in risk was greater than that identified for non-selective NSAID users (2.5 fold increased risk). From these data certain subsets of patients who at baseline are at increased risk to develop clinically significant upper GI events (including those who are aspirin users and who have a history of GDU) are particularly prone to develop complications when treated with valdecoxib.

Further Information About Clinically Significant Upper GI Events in 12 to 26 Week Controlled Arthritis Trials

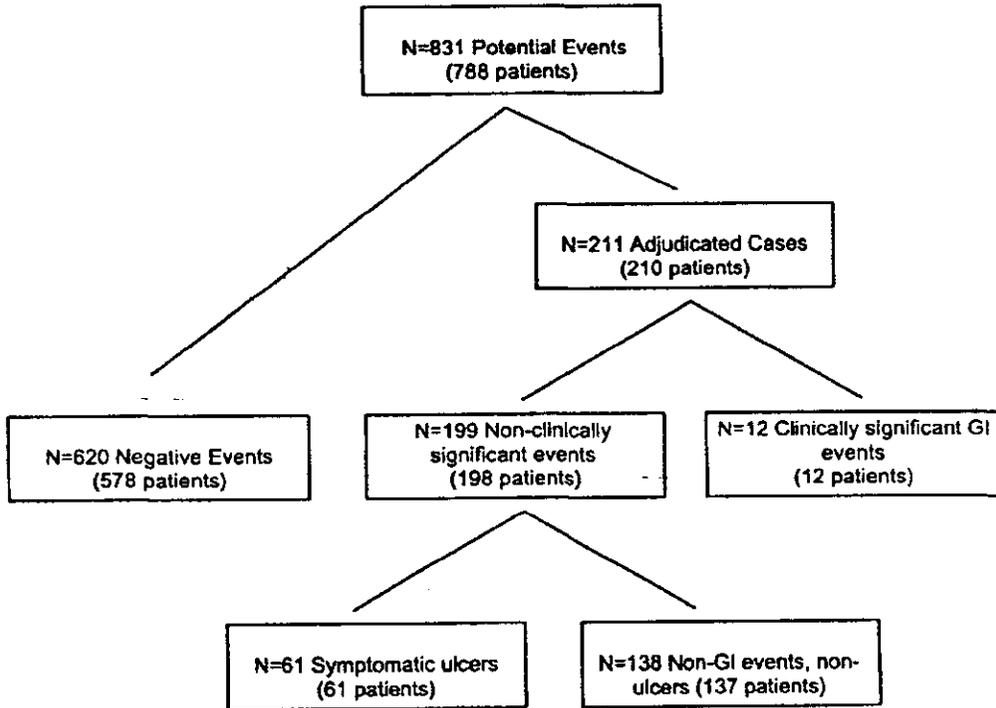
The Gastrointestinal Events Committee adjudicated 211 potential clinically significant upper GI events in the 12/26 week controlled arthritis trials. A flow-chart of the patient categorizations determined by the Committee is shown in Figure 4.

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Figure 4

**Disposition of Potential Clinically Significant UGI Events –
12- to 26-Week Controlled Arthritis Trials**



It is apparent that of the adjudicated cases 5 patients treated with valdecoxib (5 to 80 mg doses; n=3,359) were judged to be clinically significant upper GI events and 22 cases symptomatic GDUs. All five of the clinically significant events were associated with upper GI bleeding (see Table 10)

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TABLE 10

Number of Adjudicated Cases and Adjudicated Cases Meeting Pre-Specified Definitions of Clinically Significant Upper GI Events and Symptomatic Gastroduodenal Ulcers: 12- to 26-Week Controlled Arthritis Trials

Category	Placebo (n=973)	Valdecoxib 5-80 mg (n = 3359)	NSAIDs (n = 1600)
Total cases adjudicated	21	96	94
Adjudicated cases not meeting the definition of a clinically significant upper GI event or symptomatic gastroduodenal ulcer	<u>19</u>	<u>69</u>	<u>50</u>
Esophageal disease	4	11	13
Gastroduodenitis	3	13	18
Colonic or small bowel disease	2	3	2
Non-ulcer bleeding	2	16	3
Non-specific GI symptoms	4	21	9
Anemia	1	2	2
Miscellaneous	3	3	3
Adjudicated cases meeting the definition of a gastroduodenal ulcer or clinically significant upper GI event	<u>2</u>	<u>27</u>	<u>44</u>
Symptomatic gastroduodenal ulcers	2	22	37
Clinically Significant Upper GI Events	0	<u>5</u>	<u>7</u>
Upper GI bleeding	0	5	7
Perforation	0	0	0
Gastric outlet obstruction	0	0	0

Derived from Study 803 final report.

Endoscopic findings associated with these cases are summarized in Table 11.

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TABLE 11
Distributions of Clinically Significant UGI Events by Treatment Group and Category: 12- to 26-Week Controlled Arthritis Trials

Event Category	Valdecoxib 10 mg TDD (N=966)	Valdecoxib 40 mg TDD (N=845)	Valdecoxib 80 mg TDD (N=420)	Naproxen 500 mg BID (N=1197)
UGI Bleeding (Category 1)				
1A: Hematemesis with ulcer/large erosion	-	-	-	2
1B: Ulcer/large erosion with evidence of bleeding	-	-	1	4
1C: Melena with ulcer/large erosion	-	1	-	1
1D-1: Hemoccult-positive stool with ulcer/large erosion and hematocrit/hemoglobin drop	1	1	1	-
1D-2: Hemoccult-positive stool with ulcer/large erosion and orthostasis	-	-	-	-
1D-3: Hemoccult-positive stool with ulcer/large erosion and transfusion	-	-	-	-
1D-4: Hemoccult-positive stool with ulcer/large erosion and blood in stomach	-	-	-	-
UGI Perforation (Category 2)	-	-	-	-
Gastric Outlet Obstruction (Category 3)	-	-	-	-
Total	1	2	2	7

Derived from Study 803 final report. Entries are numbers of patients.

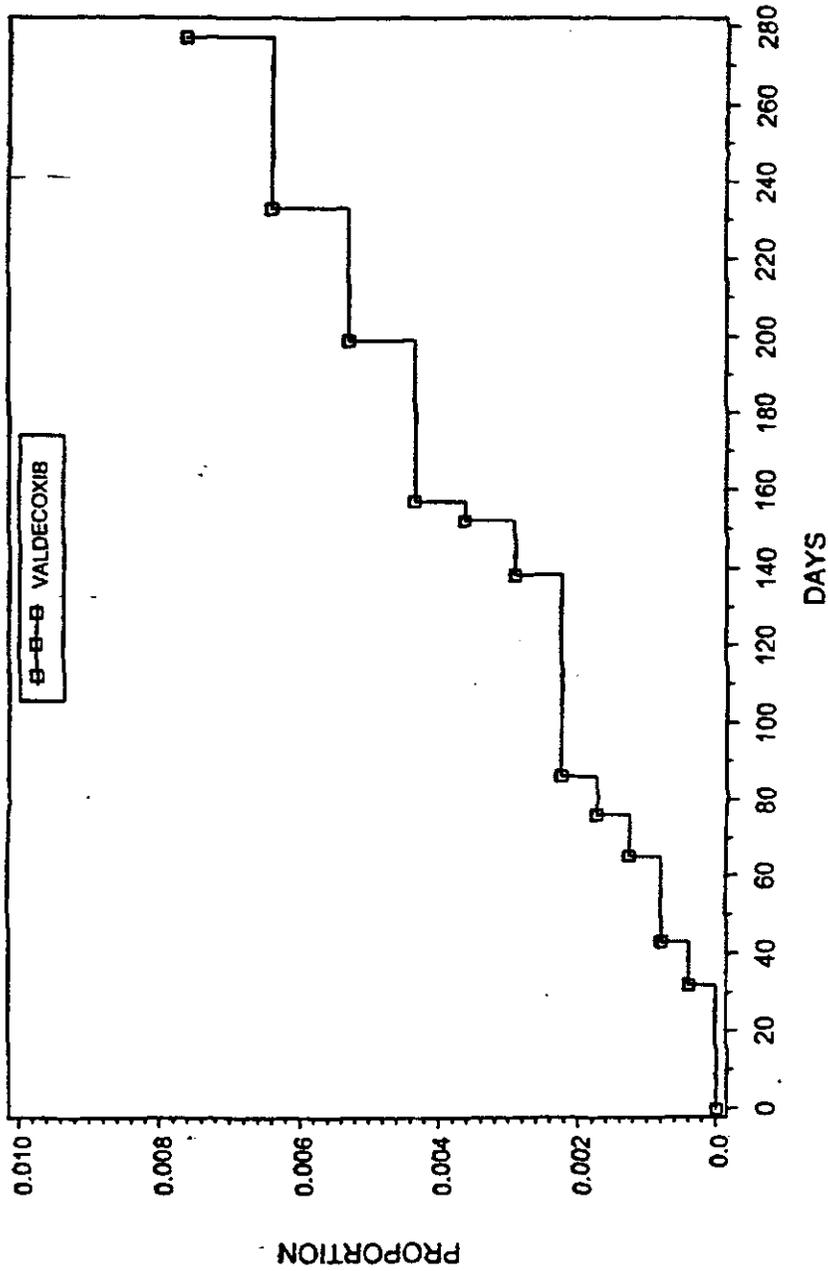
Significant ulcerated lesions associated with GI bleeding were observed in all valdecoxib dose groups (10 mg to 80 mg per day). No perforations or gastric outlet obstructions were observed. Narratives of the five cases of clinically significant upper GI bleeding associated with valdecoxib treatment are provided in Appendix 1.

From these case histories it is apparent that adaptation to long-term treatment with valdecoxib with an associated plateau in a time dependent risk to develop clinically significant upper GI events and symptomatic ulcers was not observed (see sponsor's Table T37).

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Time to Clinically Significant UGI Events and Symptomatic Ulcers
Long Term Open Label Studies
Log-Rank Test

Intent-to-Treat (ITT) Cohort



Long-Term Open Label Arthritis Studies

A total of 2,867 patients were enrolled in studies 031, 067 and 076. These patients received at least one dose of valdecoxib ranging between 10 and 80 mg daily. Their demographic characteristics are shown in Table 12.

TABLE 12
Patient Demographics, Medical History and Concurrent Medications: Long-term Open Label Arthritis Trials

Characteristic	Valdecoxib 10-80 mg/day (n = 2867)
Mean age (range), y	59.2 (18-92)
≥65 years of age (%)	36
≥75 years of age (%)	10
Women, (%)	72
Race, (%)	
White	88
Black	6
Hispanic	4
Asian	1
Other	1
Primary disease, (%)	
RA	52
Potential Risk Factor (%)	
History of GI bleeding	2
History of GI ulcer	10
Positive <i>Helicobacter pylori</i> serology (%)	
Test not performed	100
Concurrent medications, (%)	
Aspirin (≤325 mg daily)	16
Corticosteroids	31

Data derived from Tables T24, 25 and 26, Study 803 final report

It is apparent that over a third of the valdecoxib treated individuals were in the geriatric age range. Moreover, 10% of the treated patients had a history of GI ulcer and 16% were concomitantly treated with ASA. In these studies patients were not screened for *Helicobacter pylori* serological status. Adjudication by the Gastrointestinal Events Committee identified five clinically significant upper GI events in conjunction with seven symptomatic ulcers. Based on a composite of 1,352 patient years the annualized incidence of clinically significant upper GI events in valdecoxib treated patients in these long-term open label trials was 0.37%. A limitation of this analysis is that of the 2,867 patients who were tracked in the study only 41% were treated for longer than 26 weeks and 20% were treated for less than 8 weeks. Thus, although in the total group there were 1,352 accumulated patient years, the duration of drug exposure varied considerably. Therefore, the actual risk to develop clinically significant upper GI events in individuals treated for 26 weeks or longer was probably underestimated.

Not surprisingly, low dose ASA was found to exert a statistically significant effect ($p < 0.001$) on the incidence of clinically significant upper GI events in symptomatic ulcers in the long-term open label trials. The annualized incidence of clinically significant upper GI events plus symptomatic ulcers linked to valdecoxib treatment was 0.89%. In the non-aspirin users subset this incidence was 0.36%. The sponsor has attributed the lower annualized incidence rates of these events in the long-term open label trials compared to the 26 week controlled arthritis trials to the absence of scheduled endoscopies.

GI Tolerability of Valdecoxib

As shown in Table 13 certain common adverse events in the valdecoxib treatment arms of the controlled arthritis trials appear to be dose related (daily dose range between 1 and 40 mg). These include abdominal pain, nausea, flatulence, abdominal fullness and constipation.

TABLE 13
Gastrointestinal Adverse Events with Incidence $\geq 3\%$ in Any Treatment Group: Controlled Arthritis Trials

Adverse Event	Placebo	Valdecoxib (Total Daily Dose)				NSAIDs
		1-5 mg	10 mg	20 mg	40 mg	
No. treated	1142	818	1284	1012	430	1347
Dyspepsia	5.8	7.2	7.7	7.4	8.4	12.0
Abdominal pain	5.7	5.4	6.2	6.6	9.1	10.1
Nausea	5.9	5.9	6.9	6.2	7.4	7.9
Diarrhea	4.1	4.2	5.4	5.5	6.0	6.2
Flatulence	3.5	2.4	3.0	4.1	4.0	5.3
Abdominal fullness	1.7	1.2	1.9	2.2	3.3	2.7
Constipation	1.6	1.5	1.3	1.7	2.1	5.1

Derived from Table T30.1.2. All entries are percentages of patients unless otherwise specified.

Moreover, at 40 mg doses the incidence rates of abdominal pain and stomatitis were significantly higher in valdecoxib treated patients than the patients treated with placebo (see Table 14).

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TABLE 14
Analysis of GI Adverse Events between Valdecoxib (40 mg TDD)
and Placebo or Active Control: Controlled Arthritis Trials

Adverse Event	Valdecoxib*	Placebo	NSAIDs	Valdecoxib vs Placebo	Valdecoxib vs NSAIDs
No. treated	430	442	444	-	-
Abdominal pain	9.1	5.0	9.0	0.023	-
Constipation	2.1	2.3	4.7	-	0.040
Stomatitis	1.9	0.0	1.1	0.003	-

Derived from Table T6.3.2. Data are expressed in percentages of patients (except for p-values), and include any events with $\geq 1\%$ incidence in any group and a statistically significant difference ($p \leq 0.05$) between valdecoxib and either placebo or active control.

*Column includes only valdecoxib 40 mg TDD.

Nonetheless, the incidences of these symptoms were lower than those associated in the non-selective NSAID control patients, most of whom were treated with naproxen 500 mg BID. In the general surgery trials significant differences in rates of abdominal pain, constipation, nausea and vomiting were not noted between the valdecoxib 20 to 40 mg treatment groups and those treated with non-selective NSAIDs. In contrast, patients treated with oxycodone developed constipation, nausea and vomiting at significantly higher rates (Table 15).

TABLE 15
Analysis of Common GI Adverse Events: General Surgery Trials

Adverse Event	Valdecoxib 20-40 mg	Oxycodone/APAP	P value	Valdecoxib 20-40 mg	NSAIDs	P value
No. treated	337	250		408	203	
Abdominal pain	6.8	7.6	-	5.4	6.9	-
Constipation	5.6	10.4	0.041	6.4	4.9	-
Nausea	17.5	28.4	0.002	14.2	19.7	-
Vomiting	8.3	16.4	0.004	7.6	6.4	-

Derived from Tables T11.3.2 and T11.3.3. Includes Studies 010, 011, 032, 033, 037, 052, and 072. All entries are percentages of patients unless otherwise specified. Data are expressed in percentages of patients (except for p-values).

In summary

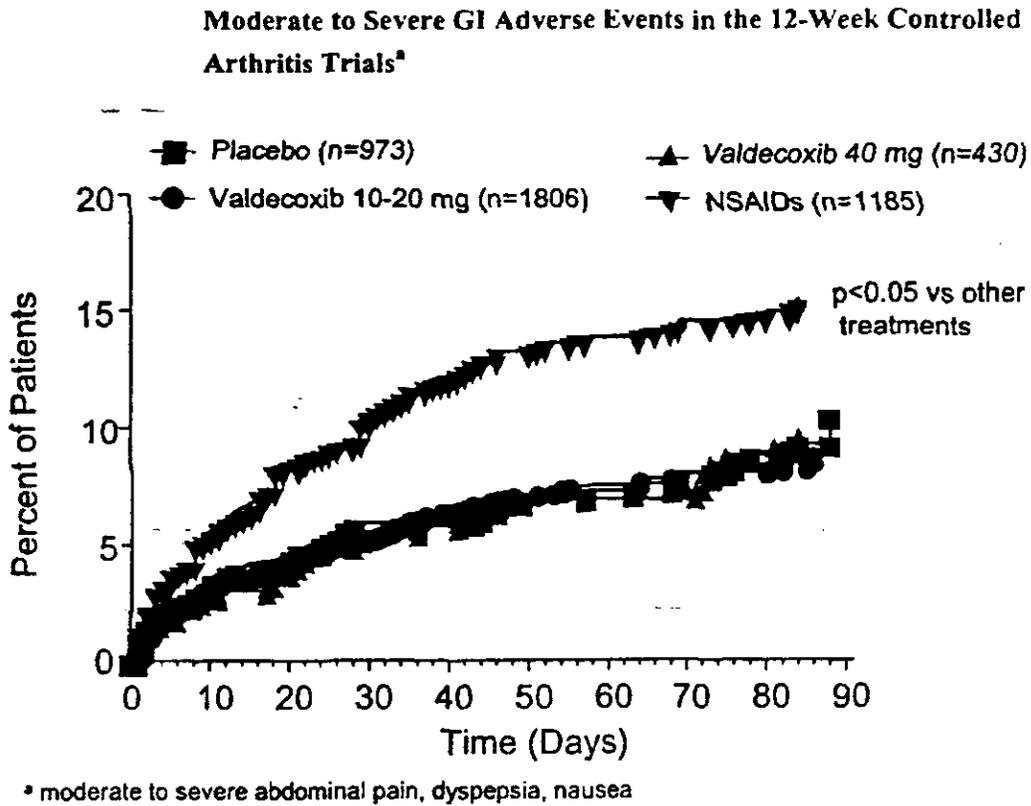
- In the 10 to 20 mg daily dose range valdecoxib treatment was associated with a statistically significant lower incidence of dyspepsia, abdominal pain, and constipation.
- At higher daily doses (40 mg — 80 mg) differences in the incidences of these adverse events in the controlled arthritis trials diminished and are not statistically significant (see Table 13).
- In the general surgery trial patients subpopulation, differences in the rates of common GI adverse events (abdominal pain, constipation, nausea and vomiting) between the valdecoxib 20 to 40 mg treatment groups and non-selective NSAIDs were not apparent.

- An analysis of GI adverse events causing withdrawal between valdecoxib treatment and the non-selective NSAID comparator groups revealed a small but statistically significant difference in the incidence of abdominal pain and dyspepsia associated with administration of valdecoxib in the 10 to 20 mg dose range. At doses of valdecoxib higher than 40 mg these differences became insignificant.
- In the general surgery trials no differences were apparent in the incidence of common GI adverse events (abdominal pain, nausea and vomiting) leading to withdrawal. In these trials the incidence of adverse events associated with non-selective NSAIDs ranged between 0 and 1%.
- A time to event analysis of moderate to severe abdominal pain, dyspepsia and nausea in the 12 week controlled arthritis trials (studies 048, 049, 053, 060 and 061) revealed that, as a composite, the incidence of these symptoms was not different than that associated with placebo and was lower than the incidence associated with non-selective NSAIDs (see Figure 5).

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Figure 5



- The incidence of these symptoms continued to increase during the 12 week period of treatment such that a time dependent resistance to side effects was not observed either in the valdecoxib or non-selective NSAID treatment arms.

Serious Gastrointestinal System Adverse Events

As previously mentioned, serious gastrointestinal system adverse events (SAEs) associated with gastro-duodenal ulcer complications were apparent in the vandecoxib controlled arthritis trials, the high dose osteoarthritis and rheumatoid arthritis trial (study 047), and the long-term open label trials. SAEs with a probable or uncertain relationship to study medication are listed in Tables 16, 17, 18 and 19.

TABLE 16
GI-Related Serious Adverse Events with an Uncertain or Probable Relationship to Study Medication Occurring During Treatment or Within 30 Days After Last Dose of Study Medication: Controlled Arthritis Trials

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity	DER Number
015/US0032-0450 PBO	54/M	30	33	Abdominal pain	Mod/Uncertain	971222-CL326
015/US0033-0462 NAP	62/M	10 10	10 (O) 10 (O)	Gastric Ulcer [†] Gastritis [†]	Severe/Probable Severe/Probable	971212-CL430
048/US0038-0231 DIC	59/F	47	50	Pancreatitis	Severe/Uncertain	990715-CL929
048/US0046-1154 DIC	71/F	23 25	25 28	Abdominal pain [†] Gastritis	Severe/Uncertain Mild/Uncertain	991102-CL242 000218-CL193
048/US0051-1118 DIC	62/F	70 70	73 73	Diarhea [†] Hematochezia [†]	Severe/Probable Severe/Probable	991215-CL470
049/US0010-0173 V10	78/F	68	74	Nausea [†]	Mod/Uncertain	990820-CL716
049/US0108-0427 NAP	50/F	37 40	39 40 (O)	Chest pain non-cardiac Abdominal pain [†]	Mod/Probable Mod/Probable	990817-CL537
060/US0120-1511 V20	73/F	9 9 9	15 15 15	Ileus [†] Nausea [†] Vomiting [†]	Severe/Uncertain Severe/Uncertain Severe/Uncertain	060210-CL621
061/US0115-1454 NAP	52/M	53 53	55 55	Gastric Ulcer GI Hemorrhage [†]	Severe/Probable Severe/Probable	000419-CL479
061/US0115-1455 V40	62/F	46 49	46 49 (O)	GI Hemorrhage [†] Anemia [†]	Severe/Probable Severe/Probable	000502-CL414

Derived from Appendix 2.1.1. [†] Patient prematurely withdrew due to this adverse event. Mod; moderate; PBO, placebo; NAP, naproxen sodium; DIC, diclofenac; V10, valdecoxib 10 mg total daily dose; V20, valdecoxib 20 mg total daily dose; V40, valdecoxib 40 mg total daily dose; O, ongoing.

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TABLE 17

GI-Related Serious Adverse Events with an Uncertain or Probable Relationship to Study Medication Occurring During Treatment or Within 30 Days After Last Dose of Study Medication: High-Dose OA and RA Trial

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
047/US0129-2724 NAP	65/F	69 77 80 80	79 (O) 79 (O) 80 (O) 80 (O)	Nausea [†] Vomiting [†] Gastroenteritis Renal Failure Acute	Mod/Probable Mod/Probable Severe/Probable Severe/Probable	000509-CL720 000517-CL629
047/US0217-0962 NAP	71/M	19 19	21 19 (O)	Duodenal Ulcer Hemorrhagic [†] Anemia [†]	Severe/Probable Severe/Probable	000103-CL895
047/US0228-0752 NAP	51/F	14 18	26 26	Melena [†] Abdominal Pain [†]	Severe/Probable Severe/Probable	000907-CL497
047/US0230-1142 V80	52/F	46	47	GI Hemorrhage [†]	Severe/Probable	000413-CL960
047/US0287-0368 NAP	77/M	25	51	Duodenal Ulcer	Severe/Probable	991202-CL934
047/US0304-2585 V80	73/M	29 29 31	38 38 56	Esophagitis [†] Anemia [†] GI Hemorrhage [†]	Severe/Probable Severe/Uncertain Severe/Probable	000202-CL012
047/US0221-0650 NAP	41/M	5 5 5 5	6 6 ongoing 6 6	Abdominal pain [†] Hematemesis [†] Hemoccult positivity [†] Nausea [†] Vomiting [†]	Severe/Uncertain Mod/Uncertain Mod/Uncertain Severe/Uncertain Severe/Uncertain	991118-CL150
047/US0304-2656 NAP	82/F	14	48	Gastroesophageal Reflux	Mild/Probable	000225-CL384

Derived from Appendix 2.1.1. [†]Patient prematurely withdrew due to this adverse event. Mod, moderate; NAP, naproxen sodium; V40, valdecoxib 40 mg total daily dose; V80, valdecoxib 80 mg total daily dose; O, ongoing (on date of last dose).

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TABLE 18
GI-Related Serious Adverse Events Related With an Uncertain or Probable Relationship to Study Medication That Occurred During Treatment or Within 30 Days Posttreatment: Long-Term Open-Label Trials

Study/ Patient ID/ Treatment	Age/ Sex	Preferred Term	Day of Onset	Day Resolved	Severity/ Attribution	DER #
031/00120055/ V10	69/F	GI hemorrhage (w/d)	54	56	Severe/uncertain	990414-CL859
031/00140006/ V20	57/M	Anemia Diverticulosis (w/d) Duodenitis GI hemorrhage	152 152 152 152	158 158 158 158	Severe/uncertain Severe/uncertain Severe/uncertain Severe/uncertain	990628-CL798
031/00160029/ V20	55F	Gastric Ulcer (w/d)	216	236	Severe/uncertain	991011-CL160
031/00220014/ V20	79/M	Gastritis (w/d) Diverticulitis	137	137	Severe/uncertain Severe/uncertain	990623-CL547
076/02290464/ V80	58/M	Gastric Ulcer (w/d) Hemorrhagic	89	96	Severe/Probable	000713-CL562
061/05051087/ V40	73/F	Gastritis (w/d) Duodenal Ulcer	65	83 (O)	Mod/uncertain Mod/uncertain	000627-CL886
061/05260925/ V20	56/M	Gastritis	18	22	Severe/uncertain	000207-CL964

Data derived from Appendix 2.2.1. w/d – indicates event caused premature withdrawal from the study; (O) ongoing (on date of last dose).

TABLE 19
GI-Related Serious Adverse Events with an Uncertain or Probable Relationship to Study Medication Occurring During Treatment or Within 30 Days After Last Dose of Study Medication: General Surgery and Opioid-Sparing Analgesia Trials

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
011/US0002-0105 Oxy/APAP	42/F	2	9	Ileus	Severe/Uncertain	991102-CL030
011/US0002-1010 Oxy/APAP	46/F	2	4	Ileus ¹	Severe/Uncertain	000119-CL708
011/US0002-1012 PBO	63/F	2	8	Ileus	Mod/Uncertain	000328-CL063
038/US0007-0155 V40	75/F	2	5	GI hemorrhage	Mild/Uncertain	000522-CL609
051/FI0001-0330 PBO	59/F	7	17	Intestinal perforation	Severe/Uncertain	000518-CL699
052/SP0004-0221 PBO	45/M	1	2	Peritonitis Vomiting	Severe/Uncertain Mod/Probable	000419-CL364

Derived from Appendix 2.1.1. ¹ Patient prematurely withdrew due to this adverse event. Mod; moderate; Oxy/APAP, oxycodone 10 mg/acetaminophen 1000 mg; PBO, placebo; V40, valdecoxib 40 mg total daily dose.

As shown in these Tables SAEs occurred during treatment or up to 30 days after the last dose. In the controlled arthritis trials a single case of GI hemorrhage associated with valdecoxib treatment was attributed to diverticulosis and angiodysplasia. Although none of the 3,544 patients treated with valdecoxib in the controlled arthritis trials (dose range between 1 and 40 mg per day)

developed serious gastrointestinal hemorrhage only 1/1,347 patients treated with non-selective NSAIDs (active comparator) developed this adverse event. This rate (less than 0.1%) is lower than the expected incidence associated with serious GI hemorrhage associated with non-selective inhibitors in a vulnerable patient population. It can be inferred that most patients who were enrolled in the controlled arthritis trials were not at high risk to develop NSAID induced upper GI hemorrhage..

In the high dose OA and RA trial (study 047) in which patients were treated for 26 weeks with valdecoxib 40 or 80 mg daily, or naproxen 500 mg BID (approximately 400 patients per treatment arm) two patients who were treated with valdecoxib 80 mg developed severe GI hemorrhage. These events were described as probably related to study medication and led to early withdrawal from the study. In the naproxen treatment arm two patients also developed severe GI bleeding and a third developed duodenal ulcer. Based on these results it appears that daily administration of 80 mg of valdecoxib is associated with a significant incidence of GI hemorrhage in an outpatient population treated for osteoarthritis and rheumatoid arthritis. This incidence does not appear to be substantially different than the incidence associated with the administration of naproxen.

Not surprisingly, in the long term trials, gastroduodenal ulcers and/or mucosal damage associated with GI hemorrhage were linked to the use of valdecoxib ranging in daily doses between 10 mg and 80 mg. There did not appear to be a relationship with duration of therapy. Although 6/7 cases were labeled as having uncertain attribution to the study drug, without a comparator arm attribution of these cases to study drug cannot be ruled out.

In the list of SAEs associated with treatment in general surgery and opioid sparing analgesia trials only one case of GI hemorrhage was associated with the use of valdecoxib (40 mg daily). It is notable that there was an absence of cases of GI hemorrhage or upper GI serious adverse events associated with the use of a nonselective NSAID comparator. These findings suggest that the patients who were studied did not manifest vulnerability to NSAID-linked ulcer complications.

Another source of serious gastrointestinal adverse events linked to valdecoxib treatment is study 035 that was recently included in NDA 21-294 seeking approval of paracoxib for intravenous administration (paracoxib is the prodrug of valdecoxib) (see Table 20).

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TABLE 20

POSTSURGICAL ANALGESIA STUDIES: GENERAL SURGERY - Continued							
Report No.: Protocol No.: Short Title: Location (Volume/Page)	Investigator(s): Study Site: Start Date: Published Study Reference:	Study Design*	No. of Subjects: Age: Range: Sex: Race:	Diagnosis and Criteria For Inclusion	Tested Agent(s)		N
					Name: Form: Route of Administration	Dosage: Strength: Duration of Treatment	
8. P: E91-99-02-052 R: E91-00-06-062	10 investigators at 10 European sites 10 December 1999	Multicenter Multi-dose Randomized Double-blind Single dose Comparator- and Placebo- controlled Parallel group	298 Randomized 298 Dosed 18-85 years 243 male 26 female 289 Caucasian	Patients who have undergone total	Valdecoxib 20 mg tablets Valdecoxib placebo Diclofenac 75 mg SR capsules Diclofenac placebo Oral administration	Valdecoxib 20 mg BID Valdecoxib 40 mg BID Diclofenac 75 mg SR BID Placebo 36 hours	88 89 85 87
9. P: N91-99-02-072 R: N91-00-06-072	Four investigators at four study sites within the United States 26 October 1999	Multicenter Single dose Multi-dose Randomized Double-blind Comparator- and Placebo- controlled Parallel group	201 Randomized 201 Dosed 20-78 years 30 Males 171 Female 182 Caucasian 25 Black 11 Hispanic 2 Asian 1 other	Patients with moderate to severe pain	Valdecoxib 20 mg IR tablets Valdecoxib placebo Oxycodone 5 mg / acetaminophen 500 mg capsules (Tylox [®]) Tylox [®] placebo Oral administration	Day 1 - Single dose of one of the below: Valdecoxib 40 mg Oxycodone 10 mg/acetaminophen 1000 mg (Tylox [®]) Placebo Days 2-4; active medication doses Q4-6h PRN (up to 80 mg daily for Valdecoxib) Valdecoxib 40 mg Oxycodone 10 mg/acetaminophen 1000 mg (Tylox [®])	88 88 88 80 42
10. P: 893-99-02-035 R: 893-00-06-035 Parcoxib / Valdecoxib Safety vs. Placebo Following Coronary Artery Bypass Graft	58 investigators at 58 sites worldwide: 12 January 2000	Multicenter Randomized Double-blind Placebo- controlled Multiple-dose Parallel-group	482 Randomized 482 Dosed 34-76 years 400 Males 82 Female 432 Caucasian 8 Black 8 Asian 8 Hispanic 1 Other	Adult males or females requiring primary coronary artery bypass graft surgery via median sternotomy	Parcoxib sodium (lyophilized) 20 mg (as parcoxib) in vials Valdecoxib 20 mg tablets Codeine 30 mg / acetaminophen 300 mg (Tylenol 3) [®] Codeine 30 mg/paracetamol/ 500 mg (Tylenol [®] , Geronide [®]) Placebo Intravenous Oral	Parcoxib sodium 40 mg IV at time of anesthesia and every 12 hours up to 72 hours; after the IV is discontinued and patient was able to take oral medication, Valdecoxib 40 mg every 12 hours; supplemental analgesic medication available both during the IV and oral treatment periods. Placebo; supplemental analgesic medication available both during the IV and oral treatment periods. 14 days	311 151

This perioperative pain control study of coronary artery by-pass graft (CABG) patients included 311 treated with parcoxib sodium 40 mg i.v. BID for up to 72 hours followed by oral valdecoxib 40 mg BID (n=311) and individuals treated with placebo in conjunction with non-COX-2 inhibitor analgesics (n=151). It is apparent that none of the serious adverse GI events occurred in the placebo arm of the 035 study. Of the nine serious outcomes, all occurred during the first 72 hours of I.V. parcoxib treatment, the subsequent phase of oral treatment with valdecoxib, or shortly thereafter. Of these cases, 5 were attributable to serious complications of peptic ulcers. In some of these cases SAEs occurred within a few days of cessation of the I.V. formulation phase of treatment. The side effects appear to be related to the sequential effects of I.V. parcoxib followed by oral valdecoxib treatment. It is possible that in some cases uncomplicated ulcers were induced during the I.V. formulation treatment phase and progressed to cause complications as a consequence of continuation of treatment with oral COX-2 inhibitors. The sponsor has pointed out that in two of these cases *H. pylori* colonization was detected. It should be emphasized that the presence of this organism does not exclude that treatment with the COX-2 inhibitor was a cause for both the formation of peptic ulcerations/lesions and the subsequent complications described above. At this time there are insufficient data to determine whether *H. pylori* infection increases the risk for complicated GDUs in these patients.

REVIEWER'S COMMENTS

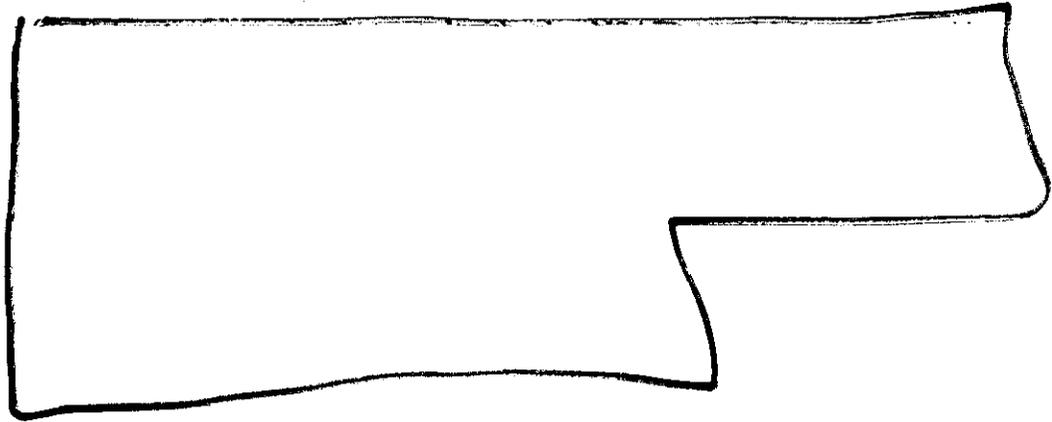
Many of the issues that surround GI safety of valdecoxib, a second generation COX-2 inhibitor, are identical with questions that have previously been raised in an analysis of the first generation COX-2 inhibitors, celecoxib and rofecoxib. It is essential that the Agency take a unified position addressing these issues in order to establish consistent guide posts for informative study designs and labeling of members of this drug class. Significant issues that should be addressed include the following:

- In demonstrating enhanced GI-safety profile COX-2 inhibitors compared to non-selective NSAIDs the sponsor has emphasized that the incidence of endoscopic ulcers/erosions measured during scheduled endoscopies is a safety endpoint. It is not clear that this surrogate measure can be used as a predictor of risk for the development of complicated and/or symptomatic ulcers which occurred at a lower frequency in predisposed individuals who manifest confounding risk factors (see above). The finding of endoscopic ulcers at a scheduled endoscopic examination (defined by the sponsor as endoscopically detected breaks in the mucosa ≥ 3 mm in diameter) has yet to be validated as a surrogate marker for clinically significant adverse events in individuals with low/high risk to develop complications or symptomatic ulcers. Since the natural course of most erosions/superficial small ulcers is characterized by transience and resolution of the mucosal injury, it is critical to know whether the incidence of gastroduodenal ulcers destined to become "bad actors" is impacted by the use of COX-2 inhibitors such as valdecoxib. There is a need to distinguish whether COX-2 inhibitors only have an impact on the incidence of mucosal injury associated with a clinically insignificant course or whether they affect the subset of individuals with lesions predisposed to clinical complications. In the case of celecoxib, the sponsor performed the CLASS study (see above). Unfortunately, although there was a trend in favor of the celecoxib treatment arm, the primary efficacy endpoint (incidence of complicated ulcers) did not achieve statistical significance. An analysis of the incidence of symptomatic and complicated ulcers (a non-prespecified composite endpoint) was carried out. The differences between celecoxib and nonselective NSAID treatment arms were inconsistent and depended on the specific nonselective NSAID comparator. Importantly, the study design did not allow for prospective assignment of risk for complicated ulcers or the composite of symptomatic and complicated ulcers in specific subsets of patients who were predisposed to complications. In the case of patients who were taking low dose aspirin, concomitant usage with celebrex increased the rates of complicated and symptomatic ulcers. In this group, celebrex did not offer an advantage over nonselective NSAIDs. Indeed, when compared to ibuprofen it may have conferred an increased risk for toxicity. With this overview the value of gastroduodenal ulcer incidence measured during scheduled endoscopies as a reliable surrogate measure has been called into question. At this time there are insufficient data to determine whether there is a reduction in the risk to develop complicated and symptomatic ulcers when the COX-2 inhibitors are compared to nonselective NSAIDs. Labeling that establishes this disclaimer and which avoids disproportionate prominence of results of ulcer measurements (most are asymptomatic) during scheduled endoscopies should be pursued with the sponsor.

- A significant limitation of the information provided in the NDA database is the under-powering of safety outcomes of individuals who may be predisposed to serious adverse events and complications associated with NSAID treatment. Co-therapies or co-morbid conditions that may increase the risk of complicated ulcers patients treated with valdecoxib include the history of prior gastroduodenal ulcers and GI bleeding, treatment with corticosteroids, anti-coagulants or other NSAIDs, old age, debilitated health status, major surgery and extended duration of treatment. Sufficient powering to study each of the aforementioned subsets is not a characteristic of the safety studies that have been provided. In the case of the endoscopic ulcer studies of geriatric subjects age 65 to 75 years treated with valdecoxib study 045 was completed. This study was limited by the fact that only 62 subjects were included in each treatment arm. In the case of the 12 to 26 week controlled arthritis trials only 2/1347 patients treated with non-selective NSAIDs developed clinically significant ulcer complications. This low incidence (0.15%) suggests that a patient population not prone to these complications was studied. These deficiencies can only be remedied by sufficiently powered safety studies. The study population should consist of patients who are at increased risk to develop complicated ulcers.
- An upper limit of 7 days was adhered to in all of the endoscopic studies of healthy subjects treated with valdecoxib (studies 017, 044, 045). Although in some of the PK studies apparently healthy subjects were exposed to longer duration of treatment, small numbers of individuals were enrolled. Therefore, at this time there are no data to assess the ulcerogenic potential in healthy subjects of continued treatment with valdecoxib beyond 7 days.
- Study 035 of patients undergoing CABG (submitted with NDA 21-294; paracoxib sodium for I.V. use) was characterized by sequential treatment of paracoxib sodium I.V. formulation for 72 hours beginning at the time of extubation, followed by oral valdecoxib treatment for 11 days. Compared to the placebo treatment group in which there were no detected ulcer complications, the paracoxib/valdecoxib treatment group revealed patients who developed serious adverse events linked to complications of gastroduodenal ulcers. Although the study was not powered to determine a precise incidence of this category of side effects, it is apparent that it can be characterized as follows:
- The patient population was particularly vulnerable to ulcer complications because it included geriatric subjects up to the age of 76 years. In addition, study enrollees were physiologically stressed as a result of the surgical procedure(s) that they underwent. Despite the fact that in some cases ulcer complications occurred during the valdecoxib phase of treatment, a significant contribution of paracoxib administered at the earlier phase must be assumed. Therefore, it can be concluded that in contrast to the minimal risk of valdecoxib treatment in healthy subjects, use of this agent as an analgesic in a physiologically stressed patients who have undergone surgery such as CABG, appear to be linked to a higher risk for the development of serious adverse complications associated with gastroduodenal ulcers. This risk may be amplified in patients who are predisposed to the development of such complications.

- The sponsor has provided a 7-point scale that quantitates petchiae/erosions/ulcers as measures in the endoscopy studies comparing effects of valdecoxib and other non-NSAID agents. The clinical relevance of this scale, considered a bioassay, which is heavily weighted toward superficial non-ulcer lesions, is dubious.
- As noted by the sponsor, abdominal pain leading to early withdrawal from studies was prevalent in all NSAID treatment arms, including the valdecoxib treatment arms. Although pain occurred with a similar frequency in the placebo treatment group, a correlation of valdecoxib-induced gastroduodenal symptomatic ulcers cannot be made in patients who did not undergo endoscopy. At this time the rate of gastroduodenal ulcers in patients who developed abdominal pain during analgesic trials is not known. This should be stated in the labeling.
- The interplay between *H. pylori* colonization/infection and valdecoxib in the causation of gastroduodenal ulcers is unknown. This should be stated in the labeling.
- The safety effects of combined aspirin or other non-selective NSAIDs and valdecoxib treatment in patients susceptible to complications of gastroduodenal ulcers have not been adequately assessed. As in the case of celecoxib, the concomitant use of ASA or other nonselective NSAIDs appeared to reverse, at least partially, any potential safety benefit of valdecoxib and may in fact have a potentiating effect on mucosal toxicity. The labeling should caution against concomitant use of ASA or other non-selective NSAIDs with valdecoxib in patients who are susceptible to the development of complications associated with gastroduodenal ulcers.
- The likelihood that COX-2 inhibitors do not appear to provide protection against cardiovascular/thrombotic safety events and/or in some cases increase the risk for these events suggests that an adequately powered study be performed to establish comparative overall safety and mortality of users of valdecoxib alone, low dose ASA alone, and the combination. In the controlled studies of OA and RA patients treated 12-26 weeks only 14% (n=470) of the valdecoxib treated patients (n=3359) were concomitantly treated with low dose ASA. The need for a sufficiently powered hazard analysis is especially important in geriatric patients who are prone to cardiovascular/thrombotic events.
- Some of the issues raised by this review can only be addressed in future studies that enroll larger numbers of patients at risk for the development of gastroduodenal ulcer complications. Studies to evaluate the risk in each of these subsets treated with valdecoxib should be planned as part of a Phase IV commitment.

/ page(s) of
revised draft labeling
has been redacted
from this portion of
the review.



6

Mark Avigan, M.D., C.M.

cc:
HFD-180/V Raczkowski
HFD-180/JKorvick
HFD-180/HGallo-Torres
HFD-180/MAvigan
HFD-181/Consult File

APPENDIX 1

Controlled Arthritis Trials

Study N91-99-02-047

Patient 0207-0211 was a 71 year old female with a history of depression, atherosclerotic cardiovascular disease, cerebrovascular ischemia, chronic obstructive pulmonary disease, asthma, gastrointestinal associated NSAID intolerance, urinary tract infection, renal calculi, hypothyroidism, and OA. Concomitant medications included conjugated estrogens, levothyroxine, citalopram, aspirin, acetaminophen, salmeterol, fluticasone, and ipatropium/albuterol. The patient was randomized to valdecoxib 40 mg BID.

After 23 days of treatment the patient began experiencing dyspepsia which was relieved by eating. The patient also reported epigastric pain and mild nausea. Laboratory examination on Study Day 43 revealed a hemoglobin of 13.6 g/dL compared with a Baseline hemoglobin of 14.3 g/dL and a hematocrit of 41% compared with a Baseline hematocrit of 45%. Stools were found to be hemocult negative on Study Days 87 and 89 but were Hemocult positive on Study Day 88. Follow-up laboratories revealed a further drop in hemoglobin and hematocrit to 12.9 g/dL and 40% respectively on Study Day 99. An endoscopy was performed on Study Day 103 revealing a 3.5 cm antral ulcer, gastritis, and duodenitis. Study medication was discontinued on Study Day 103 and the patient was withdrawn from the trial. This event was classified as: **gastric ulcer, GI bleed (1D1)**.

Study N91-99-02-047

Patient 0275-1227 was a 48 year old female with a history of hypertension, hiatal hernia, mild gastritis, duodenitis, hysterectomy, facial cellulitis, and RA. Concomitant medications included acetaminophen, prednisone, hydroxychloroquine, and nifedipine. The patient was randomized to valdecoxib 20 mg BID.

After 43 days of treatment the patient began experiencing multiple black, watery stools. Laboratory evaluation on Study Day 45 revealed a hemoglobin of 9.1 g/dL compared with a Baseline hemoglobin of 12.4 g/dL and a hematocrit of 28.0% compared with a Baseline hematocrit of 35.0%. Stools collected on Study Days 51, 52 and 53 were hemocult negative. Study medication was discontinued on day 56. An endoscopy was performed on Study Day 63 revealing two 0.8 cm and one 0.5 cm duodenal bulb ulcers. A biopsy for *Helicobacter pylori* was classified as: **duodenal ulcer, GI bleed (1C)**.

Study N91-99-02-047

Patient 0260-0357 was a 86 year old female with a history of anxiety, depression, otitis media, bilateral cataracts, bilateral macular degeneration, labil blood pressure, hysterectomy, peripheral vascular disease, left femoral-popliteal bypass surgery, right bundle branch block, angina, peripheral edema, hyperlipidemia, pneumonia, bronchitis, occult GI bleeding, constipation, abdominal pain, cholecystectomy, colon polyps, esophagitis with stricture formation, bursitis,

compression fracture of T11 and T12, and OA. Concomitant medications included alendronate, alprazolam, and aspirin. The patient was randomized to valdecoxib 20 mg BID.

After 29 days of treatment the patient began experiencing epigastric pain. Stool on Study day 31 was hemocult positive. An endoscopy was performed on Study Day 31 revealing a mildly edematous pylorus and two distal duodenal bulb ulcers measuring 0.5 cm and 1.0. The smaller of the two ulcers had a base consisting of exudative material and dried blood and the larger of the ulcers was causing some post bulbar stenosis preventing further passage of the endoscope. A biopsy for *Helicobacter pylori* was negative as was a Baseline serology. Laboratory evaluation on day 35 revealed a hemoglobin of 9.7 compared with a Baseline hemoglobin of 16 g/dL and a hematocrit was 29.0% compared with a Baseline hematocrit of 136.0%. Study medication was discontinued on day 29 and the patient was discontinued from the study on day 35. This event was classified as: **duodenal ulcer; GI bleed (1D1)**.

Study N91-99-02-047

Patient 0225-0323 was a 67 year old male with a history of tympanoplasty, sciatica, sinus bradycardia, hyperlipidemia, hiatal hernia with surgical repair, ileal ulcers, hemorrhoids, constipation, colonic polyps, GERD, gastroduodenal ulcers, NSAID intolerance, cholecystectomy, and OA. Concomitant medications included glucosamine, garlic, ginko biboba, saw-palmetto, vitamins E and C, simvastatin, atorvastin, famotidine, atenolol, cyclobenzaprine, diflorasone diacetate, and aspirin. The patient was randomized to valdecoxib 40 mg BID.

After 117 days of treatment the patient began experiencing intermittent dyspepsia which was relieved by eating. The patient completed the study and took the last dose of study medication on Study Day 161. The patient had not reported the dyspepsia until day 162. An endoscopy was performed on day 162 revealing a deep 1.2 cm ulcer on the lesser curvature of the antrum with visible blood present, and 6-10 erosions in the duodenal bulb. A biopsy for *Helicobacter pylori* was negative as was a Baseline serology. Blood work on the day of the endoscopy revealed a hemoglobin of 13.6 g/dL compared with a Baseline hemoglobin of 13.7 g/dL and a hematocrit of 39.0% compared with a Baseline hematocrit of 38.0. This event was classified as: **gastric ulcer; GI bleed (1B)**.

Study N91-99-02-049

Patient 0092-0070 was a 44 year old female with a history of chronic reflux esophagitis, pyloric erosion, gastroduodenal ulcers, hysterectomy, bladder repair, osteoporosis and OA. Concomitant medications included estropipate, calcium, and halibut liver oil. The patient was randomized to valdecoxib 10 mg QD.

After 15 days of treatment the patient was found to have a decreased hemoglobin and hematocrit. Specifically, the hemoglobin was 13.0 g/dL compared with a Baseline of 14.6 g/dL and the hematocrit was 37.0% compared with a baseline of 43.05. On study day 17 the patient reported nausea and study medication was discontinued. A follow-up laboratory evaluation on study day

19 again revealed a hemoglobin of 13.0 g/dL with a hematocrit of 38.0%. A stool sample collected on day 19 was Hemoccult positive. On study day 23 a physical examination revealed both epigastric and right upper quadrant tenderness. On study day 29 an endoscopy was performed revealing a normal esophagus, 2 -5 petechiae, 2-5 antral erosions, a 0.5 cm antral ulcer with surrounding edema, and a normal appearing duodenal bulb and descending duodenum. A biopsy for a CLOtest was negative. The patient was withdrawn from the study. This event was classified as: **gastric ulcer, GI bleed (1D1)**.

**APPEARS THIS WAY
ON ORIGINAL**

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