

**Parecoxib Sodium**

**NDA 21-294**

**Medical Officer Review**

**Submission Date:** September 11, 2000  
**Received Date:** September 12, 2000  
**Review Date:** December 1, 2000

**Drug Name:** Xaptek™  
**Generic Name:** parecoxib sodium  
**Chemical Name:** sodium salt of N-[[4-(5-methyl-3-phenylisoxazol 4-yl)phenyl]sulfonyl]propanamide

**Applicant:** G.D. Searle & Co.

**Related Reviews:** Statistics, Cardio-Renal, Gastrointestinal, Biopharm, Chemistry, Pharmacology, Medical (valdecoxib)

**Pharmacologic category:** COX-2 inhibitor (parenteral)

**Proposed Indication:** Management of pain (postoperative and preemptive)  
Opioid Sparing

**Dosage forms and route:** For injection, 20 and 40 mg

**Submission type:** Original NDA

**Materials Reviewed:** **Primary documents-** N93-00-07-815  
N93-00-07-816  
N93-00-07-804  
I93-00-06-035

Orig NDA # 21-294  
HFD-550/Div File  
HFD-550/PM/Schmidt  
HFD-550/Pharm/Yang  
HFD-550/Chem/Bhavnagri  
HFD-550/Biopharm/Bashaw  
HFD-550/Statistics/Lin  
HFD-550/MO/Witter/Goldkind

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(James Witter, M.D., Ph.D.      Medical Officer)

## **Parecoxib Executive Summary**

### **Significant Issues**

- Parecoxib is a new molecular entity and represents the first parenteral “COX-2 selective” agent to seek approval in the U.S.
- Although the single dose data in several surgical situations have established that parecoxib sodium at 40 mg is efficacious compared to placebo, this is not the case for single doses of 20 mg.
- Multiple dose data with parecoxib sodium are limited and do not allow for characterization of the safe and effective dose, or dosing interval after the first dose.
- The proposed labeling claims for management of postoperative pain or for the preemptive treatment of pain or for opioid sparing with parecoxib sodium are not supported by the data available in this NDA either due to insufficient data or lack of replication of results.
- Safety data from the CABG trial suggest that certain subgroups of patients may be at increased risks for serious adverse events. Furthermore, these data can not exclude the possibility of an important safety liability associated with parecoxib sodium, particularly with repeated doses, over placebo.

### **Highlights**

- Parecoxib sodium is a parenteral prodrug of the orally available compound valdecoxib which is under concurrent review. This dual development has impacted, and confounded, the ability to make clear distinctions in terms of the safety and efficacy associated with parecoxib sodium.
- Most (approximately two thirds) of the data on safety and efficacy in the original NDA were obtained from patients or subjects exposed to single doses of parecoxib sodium. While such data is fundamental to supporting the efficacy and safety of parecoxib sodium, it is insufficient to fully characterize the safety and efficacy of this compound.
- It is unclear, from the currently available data, whether the efficacy associated with parecoxib sodium in a surgical setting is sufficient to balance the observed adverse events. However, owing to the nature of the surgical setting or use of medications both during and after the surgery, interpretation of adverse events is not always

straightforward. There are no data regarding the use of parecoxib sodium in an emergency or trauma-like setting.

## **BACKGROUND AND OVERVIEW:**

In acutely painful conditions, parenteral administration of analgesic medication can provide a rapid and sustained onset of analgesia, especially in patients unable to ingest or tolerate oral medication. Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are

commonly used parenteral analgesics for the management of acute pain. However, their use can be limited by a wide spectrum of adverse effects. These adverse effects can actually slow the postoperative rehabilitation process and compound the risk inherent in any surgical procedure. These adverse outcomes may be particularly true for elderly patients, patients with a history of peptic ulcer disease, patients in whom respiratory depression should be avoided, patients with an increased susceptibility to perioperative bleeding, and patients with compromised renal function.

Parenteral opioids are the mainstay of acute postoperative pain management in the inpatient setting. However, a number of frequent adverse effects associated with their use have been identified. These include: respiratory depression, nausea, vomiting, sedation, urinary retention, constipation, decreased gastrointestinal (GI) motility, and paralytic ileus. These adverse effects often impede postoperative rehabilitation and limit their use in the ambulatory surgical setting. Failure to provide adequate management of pain, either due to inadequate analgesic efficacy or sub-optimal treatment due to concerns about potential adverse effects, can contribute substantially to reduced quality of life among patients experiencing acute pain. Due to the growing number of outpatient surgical procedures, additional symptoms such as **somnolence and dizziness** that frequently accompany the use of opioids may further limit these agents as a treatment for postoperative analgesia, particularly in an outpatient setting.

The current standard of care for analgesia in the perioperative setting consists of opioids, with adjunctive use of NSAIDs (“multimodal analgesia”). In less severe cases, NSAIDs alone are sufficient to provide effective postoperative analgesia. The selection of multimodal drug therapy (including opioids and NSAIDs) for the management of acute pain is based on a number of principles, including the analgesic efficacy of centrally acting opioids, the peripheral anti-inflammatory and analgesic effects of NSAIDs, and the synergy that can be observed between these two modes of treatment. Although both opioids and NSAIDs are effective analgesics, neither are without safety and tolerability concerns that may become exaggerated in an already compromised postsurgical patient population.

Toradol® (ketorolac tromethamine) is currently the only approved parenteral NSAID for use in the United States. It is effective and may be used as an adjunct to opioids for the management of postoperative pain. However, the use of ketorolac is associated with a number of adverse effects characteristic of NSAIDs, including upper GI ulceration and bleeding (particularly in the elderly), reduction in renal function, hemostatic impairment

(decrease in platelet aggregation and increase in duration of bleeding), and bronchospasm. Owing to concerns about safety, the use of ketorolac has been limited to five days and cannot be administered preoperatively.

Parecoxib sodium (SC-69124A; C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>SNa) is a water-soluble inactive prodrug of valdecoxib (SC-65872), a highly selective inhibitor of cyclooxygenase-2 (COX-2). Parecoxib sodium was developed as a parenteral analgesic for the management of acute pain. It is chemically designated as the sodium salt of N-{{4-(5-methyl-3-phenylisoxazol-4-yl)phenyl}sulfonyl}propanamide. Parecoxib sodium is rapidly (T<sub>1/2</sub>=15-30 min) and essentially completely converted via enzymatic hydrolysis to the pharmacologically active moiety valdecoxib [4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide] and propionic acid. This enzymatic conversion occurs primarily in the liver. The terminal half-life (T<sub>1/2</sub>) of valdecoxib is approximately 8 hours. Following intravenous (IV) administration of parecoxib, peak (T<sub>max</sub>) plasma levels of valdecoxib are achieved in approximately 30 minutes; for intramuscular (IM) injection, peak plasma levels are achieved in approximately 1 hour.

Parecoxib sodium is supplied as a sterile, preservative-free, lyophilized powder equivalent to 20 mg or 40 mg parecoxib in single-use vials. Inactive ingredients include dibasic sodium phosphate heptahydrate, and phosphoric acid and/or sodium hydroxide (which might be added to adjust the pH to 8.0). Parecoxib sodium is designed to be reconstituted with 1 mL (20 mg vials) or 2 mL (40 mg vials) sterile saline for injection (0.9% sodium chloride).

Based on the in vitro inhibition of recombinant human COX-1 (IC<sub>50</sub>=140 μm) and COX-2 (IC<sub>50</sub>=0.005 μm), valdecoxib (the active moiety of parecoxib sodium) exhibits approximately 28,000-fold selectivity for COX-2 versus COX-1. On the basis of its COX-2 specificity of valdecoxib, it was hypothesized that parecoxib would provide a superior therapeutic index compared to currently approved conventional ketorolac and mild opioids and yield significant benefits for patients who require relief of acute pain.

According to the Sponsor, as a novel COX-2 specific parenteral agent, parecoxib has been developed to have an improved safety profile (particularly with respect to the absence of respiratory depression, lack of sedative effects, absence of effects on platelet function, and absence of UGI ulceration). The demonstration that a compound has analgesic efficacy for moderate to severe pain along with improved safety relative to currently available alternatives would represent a valuable addition to the therapeutic armamentarium for acute pain management. Parecoxib was designed to meet an unmet medical need of an efficacious anti-inflammatory parenteral analgesic that would reduce or eliminate the deleterious side effects that accompany opioid analgesics or conventional NSAIDs such as ketorolac tromethamine.

The goal of the **nonclinical pharmacology** program emphasized models in which pain and inflammation were mediated primarily by prostaglandin production via COX-2. The efficacy of parecoxib in animal models of inflammation and pain was consistent with its conversion to valdecoxib in vivo. In dose-response comparisons, parecoxib and

valdecoxib exhibited identical efficacy. In models of surgery-induced nociception, the efficacy of IV parecoxib appeared comparable to that of ketorolac tromethamine.

The safety pharmacology studies of parecoxib included neurobehavioral assessments in the rat, hemodynamic assessments in the dog, renal assessments in the rat and dog, and cardiopulmonary assessments in the guinea pig. The adverse effects of parecoxib seen in these studies suggested this agent would not be associated with adverse pharmacological effects at clinically relevant exposures. Parecoxib was also evaluated for its potential to produce acute lethality, multidose toxicity in rat and dog, GI toxicity in the rat and dog, reproductive toxicity in rat and rabbit, and in vitro and in vivo mutagenicity. Results from these studies showed that parecoxib is not expected to pose any increased risk in humans for lethality, multidose toxicity, GI toxicity, or mutagenicity.

Studies included in the NDA that discussed efficacy included fourteen double-blind, placebo controlled trials, conducted in patients experiencing pain associated with oral surgery, gynecologic surgery, orthopedic surgery, or coronary artery bypass graft (CABG) surgery. All 36 studies involving parecoxib that were included in this NDA are briefly summarized in **Table 1**.

#### **Integrated Summary of Safety**

This ISS is not intended to be the only review of the safety of parecoxib although it does attempt to integrate all relevant safety information; this relates to the nature of the compound and how the review of this NDA was divided. Therefore, the safety review of the this NDA has been addressed as follows and the interested reader should also see these other reviews:

Mark Avigan, M.D.	UGI Safety Review
Anne Farrell, M.D.	Platelet Safety Review
Douglas Throckmorton, M.D.	Renal and CV Safety Review

The intent of the following sections is to look for trends suggesting an increased incidence of a given adverse event, based on multiple line of (indirect) evidence. This is, of course, the nature of a safety review.

*Reviewer's comment: In order to obtain a more robust picture of the safety of parecoxib, certain of the trials that included valdecoxib will also be reviewed.*

#### **Study 035-Coronary Artery Bypass Graft (CABG):**

*Reviewer's comment: Owing to the unique role that the CABG trial has in this NDA, this trial will be reviewed separately.*

Study 035 was designed to evaluate the general safety and analgesic efficacy of parecoxib

and valdecoxib in patients who had undergone a first-time, isolated, coronary artery bypass graft (CABG) via median sternotomy. Patients (N=462) were randomized to receive placebo (N=151) or active (N=311) treatment, which consisted of IV or IM parecoxib 40 mg every 12 hours for at least 72 hours, followed by oral valdecoxib 40 mg every 12 hours, for a minimum total of 14 days. Both placebo and active treatment groups received standard of care medication in addition to study medication, with supplementary pain medication (morphine during the IV phase and codeine 30 mg/acetaminophen 300 mg [Tylenol #3 ®] or, at ex-US sites, codeine 30 mg/paracetamol 500 mg [Tylox ®, Gelonida ®]) available throughout the trial. **Per the study protocol, all patients were required to be taking low dose aspirin (<325 mg daily) during the study. Over 90% of the patients were in compliance with this requirement.**

Patients who participated in the CABG study were as follows for the placebo and the parecoxib/valdecoxib treatment groups, respectively:

- angina, 92.7 and 90.7%
- hypertension, 77.5 and 71.4%
- congestive heart failure, 3.9 and 4.5%
- atherosclerotic cardiovascular disease, 83.4 and 85.5%
- cerebrovascular disease (transient ischemic attacks and cerebrovascular accidents), 4.6 and 5.8%
- diabetes mellitus, 19.9 and 22.8%
- hyperlipidemia, 62.9 to 64.6%

***Reviewer's comment: The treatment groups appear to be balanced with regards to these risk factors and co-morbid conditions.***

Evaluation of safety was the primary objective of this study. Due to the complexity of post-operative medical-surgical care and the potential for the occurrence of a large number of events which are routine post-CABG surgical occurrences, a 5-member independent committee was established to review the adverse data on a selected number of "Clinically Relevant" adverse events (CRAEs). CRAE members did not participate as investigators in this trial. A "Parecoxib 035 -CABG study algorithm" was used as a guide in forwarding case materials to the CRO safety specialist. These CRAEs were defined as follows:

- **Death**
  - All cause death following randomization within 30 days of last dose of study drug
- **Cardiovascular Events**
  - **myocardial infarction. New onset (post-randomization) myocardial infarction diagnosed by finding at least two of the following four criteria:**
    - Prolonged (>20 min) typical chest pain not relieved by rest and/or nitrates
    - Enzyme level elevation, either by:
      - CK-MB >5% of total CPK
      - CK greater than 2x normal
      - LDH subtype 1 > LDH subtype 2
      - troponin >0.2 micrograms/ml

- New wall motion abnormalities
- Serial ECG (at least two) showing changes from baseline or serially in ST-T and/or Q waves that are 0.03 seconds in width and/or > or + one third of the total QRS complex in two or more contiguous leads
- **severe myocardial ischemia**
  - an acute event characterized by the onset of ischemic ECG changes in an ECG done for a specific clinical event, which resolve over time without reaching the above definitions of myocardial infarction
- **cerebrovascular accident (CVA, TIA, or hemorrhage)**
  - a new onset central neurologic event of either focal or global nature, with unequivocal physical or cognitive findings, which may be accompanied by a confirmatory diagnostic test (angiography, MRI, brain scan).
- **peripheral arterial occlusion**
  - a new clinical event characterized by clearly reduced pulses or with evidence of regional ischemia, accompanied by a confirmatory arterial vascular study (invasive or non-invasive). In the absence of a positive diagnostic test, the suspicion must be sufficiently compelling to require specific medical treatment (aggressive anti-coagulation) or surgical intervention.
- **deep vein thrombosis**
  - a syndrome consisting of increased unilateral or bilateral leg swelling, warmth and edema, with confirmatory documentation based on a positive diagnostic test (venous ultrasonography, angiography, magnetic resonance imaging, radionuclide scan or impedance plethysmography). In the absence of a positive diagnostic test, the suspicion must be sufficiently compelling to require full dose anti-coagulation.
- **pulmonary embolism**
  - an event consisting of chest pain or dyspnea and/or hypoxemia with confirmatory angiography or ventilation-perfusion scanning (high probability V/Q scan or moderate probability V/Q scan with compelling clinical picture).
- **Pericarditis**
  - a clinical event consisting of an evolving, non-ischemic pattern of PR, ST segment and

T-wave changes without evolution of a new Q waves, without accompanying significant myocardial enzyme elevation. Clinical symptoms consisting of chest pain, a rub, or fever may or may not be present. Imaging studies, if performed, show no evidence of new wall motion abnormalities, myocardial ischemia or infarction. Therapeutic intervention (e.g., NSAIDs or steroids), in the absence or additional information, does not establish the diagnosis.

- **Congestive Heart Failure (new onset or exacerbation)**
  - due to the complexity of identifying the precise etiology of new onset or exacerbation of congestive heart failure in a clinical trial setting wherein study volunteers are receiving parenteral fluid administration during the time of study drug use, the adjudication of this adverse event occurrence was divided into two time frameworks: a) During the post-operative phase of parenteral fluid administration and for 96 hours following discontinuation of parenteral fluid administration; b) commencing at a point 96 hours following discontinuation of parenteral fluid administration and through to the end of study. This “time framework” division of the study was intended to provide an opportunity to assess the occurrence of primary cardio-pulmonary destabilization as a cause of heart failure versus a study drug effect upon

the kidney producing salt and water retention with subsequent congestive heart failure. The diagnosis of new onset or worsening of congestive heart failure was made by standard clinical assessment of relevant medical history, physical, radiological examination and hemodynamic monitoring, together with blood chemical evaluation and confirmation of myocardial function impairment by one or more standard cardiac imaging techniques (such as echocardiography).

- **Renal Failure/Dysfunction**

- **Reduced Renal Perfusion/Filtration**

- in the absence of acute hypovolemia due to a nonrenal cause, other causes of reduced renal perfusion, obstructive uropathy, or other documented alternative cause of intrinsic renal disease, the presence of any one of the following would be defined as reduced renal perfusion/filtration event:

- An increase of serum creatinine >30% if baseline creatinine >0.9 mg/dL (or >1.2 mg/dL if baseline creatinine <0.9 mg/dL) and verified by a second determination
      - BUN > 200% from baseline or, with a baseline value in the upper limit of normal an absolute value >50 mg/dL and verified by a second determination
      - An absolute serum creatinine >1.7 mg/dL and BUN >45 mg/dL verified by second determination
      - Acute renal failure of recent onset as shown by hospital evaluation

- **Systemic fluid, electrolyte, and metabolic abnormalities**

- In the absence of other obvious causes, the presence of the following would be defined as a fluid, electrolyte and metabolic abnormality:

- Serum potassium >6.0 mEq/L (verified)
      - Serum sodium <130 mEq/L (verified)
      - Serum bicarbonate <20 mEq/L and chloride >110 mEq/L and other evidence of tubular dysfunction (elevated urinary amino acid excretion or elevated urinary beta-microglobulin excretion or inappropriately high urine pH or abnormal serum potassium)
      - New onset, sustained urinary dipstick proteinuria (3+ or greater magnitude (verified by a second determination)
      - New onset or worsening of edema of distal extremities or generalized edema as evidenced by either of the following:
        - weight gain of >2 kg and an increase in 1+ on a semi-quantitative clinical assessment of edema (1+ to 4+ scale) verified by a second determination
        - any report of edema with evidence of a clinical consequence (an increase of systolic blood pressure > 20 mm Hg or an increase of diastolic blood pressure > 10 mm Hg on two consecutive daily determinations or two-consecutive visits; initiation or increase in daily dose of diuretic or antihypertensive drugs to treat edema; discontinuation of study drug to treat the edema.

- **Interference with blood pressure regulation**

- In the absence of alternative medicinal, volumetric or other clinical interventions or evidence of medical noncompliance, dietary indiscretion with respect to salt intake, superimposed alternative cause for secondary hypertension, or a concurrent condition necessitating use or change in diuretics/antihypertensives, the presence of any one of the following would be defined as a renal event of the NSAID-induced interference with blood pressure regulation type:
      - An increase of systolic blood pressure  $\geq 20$  mm Hg and  $\geq 140$  mm Hg or an increase of diastolic blood pressure  $\geq 10$  mm Hg and  $\geq 90$  mm Hg on two consecutive daily determinations

- Any increase in systolic or diastolic blood pressure accompanied by the initiation of antihypertensive medication
- Any increase in systolic or diastolic blood pressure accompanied by the escalation of antihypertensive drug therapy (e.g., increase in dose, addition of a new agent, substitution of a more potent agent)
- **Glomerular or Tubulo-interstitial Disease**
  - A condition which resolves all or in part upon discontinuation of drug and which occurs in the absence of other causes of glomerular or tubulo-interstitial disease is defined as a glomerular or tubulo-interstitial renal event by the presence of the following:
    - Proteinuria >3+ or greater verified by a second determination
    - Active urinary sediment (hematuria, excess tubular epithelial cells, or pyuria)
    - Histopathologic or imaging evidence of glomerular or tubulointerstitial disease
    - Evidence of renal dysfunction as manifested by one of the following:
      - An increase of serum creatinine >30% if baseline creatinine > 0.9 mg/dL (or  $\geq 1.2$  mg/dL if baseline creatinine  $\leq 0.9$  mg/dL) and verified by a second determination
      - An increase of BUN >200% from baseline or, with the baseline value in the upper limit of normal, an absolute value  $\geq 50$  mg/dL and verified by a second determination
      - A serum creatinine  $\geq 1.7$  mg/dL and BUN  $\geq 45$  mg/dL verified by second determination.
- **Gastrointestinal Event (bleeding, perforation or obstruction) consisting of the following nine categories:**
  - UGI Bleeding (one of seven traditional clinical presentations):
    - Hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray
    - A gastric or duodenal ulcer or large erosion proven by endoscopy with evidence of active bleeding or stigmata of a hemorrhage (visible vessel or attached clot to base of an ulcer)
    - Melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray
    - Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by a fall in hematocrit of > 5% or a reduction of hemoglobin of  $\geq 1.5$  g/dL from baseline
    - Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by orthostasis (changes to postural vital signs; increase in pulse rate of >20 beats/min and/or a decrease in systolic blood pressure of >20 mm Hg and/or diastolic blood pressure of >10 mm Hg)
    - Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by a need for blood transfusion of two or more units
    - Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by blood in the stomach as determined by endoscopy or nasogastric aspiration. A separate analysis assigning suspected UGI bleeding events to one of the following alternate categories will also be done:
    - Hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray, and

- a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) < pre-bleed hemoglobin (within assay variability) or
    - hypotension (defined as less than 90/60) or orthostatic hypotension
  - A gastric or duodenal ulcer or large erosion proven by endoscopy with evidence of active bleeding or stigmata of recent hemorrhage (visible vessel or attached clot to base of an ulcer) and
    - a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) < pre-bleed hemoglobin (within assay variability) or
    - hypotension (defined as less than 90/60) or orthostatic hypotension
  - Melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray; and
    - a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) < pre-bleed hemoglobin (within assay variability); or
    - hypotension (defined as less than 90/60) or orthostatic hypotension
  - Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray, and
  - hypotension (defined as less than 90/60) or orthostatic hypotension
  - **UGI Perforation**
    - An opening in the wall of the stomach or duodenum requiring surgery, or laparoscopic repair but only if the evidence is unequivocal (free air, peritoneal irritation signs, etc.)
  - **Gastric Outlet Obstruction**
    - Opinion of clinician with endoscopic or UGI barium x-ray documentation. Endoscopic evidence would include tight edematous pylorus with an ulcer in the pyloric channel, inability to pass the endoscope tip into the duodenal bulb or descending duodenum, or retained fluid/food in the stomach. UGI barium x-ray evidence of obstruction would include; (1) a dilated stomach, (2) a slowly emptying stomach in a patient with clinical evidence of outlet obstruction and in some instances with an ulcer seen in the channel or duodenal bulb or (3) severe narrowing and edema obstructing the outlet of the stomach. Ulcers documented by endoscopy or UGI barium x-ray and with no evidence of GI bleeding will be summarized separately as will other symptomatic GI complaints.
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- **Major non-GI bleed (requiring transfusion)**
    - New onset post-randomization bleeding due to a non-GI source (single or multi-site) accompanied by either transfusion of 2 or more units of PRBCs, or a Hgb drop of 3 gm/dL or greater, (or 9 hematocrit points) which is unrelated to the sequelae of hemodilution.
  - **Infection (requiring institution of antibiotics)**
    - A documented or suspected infectious process (based on a documented constellation of signs and symptoms, with suspected source), requiring new antibiotic or antiviral therapy or a change in pre-existing antibiotic regimen.
  - **Pulmonary complications (non-infectious)**
    - atelectasis or decline in respiratory function, requiring intervention consisting of non-routine post-operative respiratory care (e.g., bronchoscopy, reintubation, or non intubation ventilatory modalities)
    - development of new, persistent (beyond 72 hours) non-LLL, symptomatic non-infectious infiltrates

- pleural effusion requiring drainage or which compromise pulmonary function as manifested by dyspnea or other discrete symptoms of respiratory compromise or which requires anti-inflammatory therapy
- ARDs or other forms non-cardiac pulmonary edema
- pneumothorax or persistent air leak

The "Events Committee" reviewed all AEs (blinded to treatment assignment) submitted by investigators which potentially meet any of the above categories. The committee verified that the AE meet pre-defined definitions, and made a judgment whether the event was "probably, possibly or remotely related" or "not related" to study drug treatment and the date of onset of the event.

***Reviewer’s comment: As noted above, a 4-member (external) Gastrointestinal Events Committee (GEC) and Renal Events Committee (REC) were also established for this study. Of note, no events in the valdecoxib “long-term” safety study (91-048) were adjudicated by the GEC to be clinically significant.***

**Table 66** summarizes the duration of exposure to either parecoxib or valdecoxib in study 035. As noted earlier, patients were given parecoxib for the first 3 days after surgery (IV dosing period) and they were then switched to oral valdecoxib. Also noted earlier, most of the patients in this trial were male (85%), Caucasian (93%) with an approximate mean age of 60 years.

**Table 66: Duration of Exposure: CABG Surgery Trial (035)<sup>1</sup>**

Days	Placebo (%)	Parecoxib/Valdecoxib 40 mg Q12H (%)
1-4	22 (15)	40 (13)
5-7	6 (4)	15 (5)
>7	123 (81)	256 (82)
Total	151	311

<sup>1</sup> From Table T.3.3, N93-00-07-816.

**Incidences of Clinically Relevant Adverse Events (CRAEs)**

**Table 67** summarizes the clinically relevant adverse events as defined and adjudicated by the events committee discussed above. During the IV dosing period, 11.6% of parecoxib /valdecoxib patients and 9.3% of placebo patients had a CRAE; these incidences were comparable to each other. During this time period, the most commonly occurring individual CRAEs were renal failure/dysfunction, infection requiring antibiotics, and pulmonary complications. Although not statistically significantly different, the number of deaths, myocardial infarctions, cerebrovascular accidents, pulmonary embolisms, along with renal and pulmonary complications were numerically more frequent for parecoxib during the IV dosing period. During the entire study period, 25.7% of parecoxib/valdecoxib patients and 15.2% of placebo patients had a CRAE; this difference was statistically significant. All events listed, with the exception of myocardial infarctions and major non-GI bleeds, were numerically more frequent for parecoxib/valdecoxib during the entire study period.

**Table 67: Incidence of Clinically Relevant Adverse Events (CRAEs)- Study 035<sup>1,2</sup>**

Event	Placebo (N=151)		Parecoxib/Valdecoxib 40 mg (N=311)	
	IV Dosing Period	Entire Study	IV Dosing Period	Entire Study
Any Event (%)	14 (9.3)	23 (15.2)	36 (11.6)	80 (25.7)*
Death	0.0	0.0	2 (0.6)	4 (1.3)
Myocardial infarction	0.0	1 (0.7)	1 (0.3)	1 (0.3)
Cerebrovascular accident	0.0	1 (0.7)	5 (1.6)	9 (2.9)
Deep vein thrombosis	0.0	0.0	0.0	3 (1.0)
Pulmonary embolism	0.0	0.0	1 (0.3)	2 (0.6)
Congestive heart disease	0.0	1 (0.7)	0.0	4 (1.3)
Pericarditis	0.0	1 (0.7)	2 (0.6)	4 (1.3)
Renal failure/dysfunction	6 (4.0)	7 (4.6)	21 (6.8)	29 (9.3)
GI event	0.0	0.0	0.0	4 (1.3)
Major non-GI bleed	2 (1.3)	2 (1.3)	0.0	0.0
Infection	6 (4.0)	11 (7.3)	3 (1.0)	29 (9.3)
Pulmonary complication	2 (1.3)	4 (2.6)	6 (1.9)	19 (6.1)

1 Derived from Table 9g and Table T5.7.1, N93-00-07-816. Numbers in () are percentages.

2 \* p-value by Fischer's exact test = 0.012. There were no other statistically significant results noted by the sponsor.

*Reviewer's comment: Of a total of 13 myocardial infarctions (Figure 8b, I93-00-06-035), 11 events (2-placebo, 9-parecoxib/valdecoxib) were sent to the Events committee for adjudication. Only 2 events (patient 1128-placebo; patient 0130-parecoxib/valdecoxib) were adjudicated as meeting the predefined criteria for a CRAE as noted in the table above. Of the nine remaining events (1-placebo, 8-parecoxib/valdecoxib) all were felt to either have occurred prior to drug or did not meet the criteria. One event that was felt not to meet criteria in the parecoxib/valdecoxib group was a death (patient 1136, see appendix of this review for summary). Owing to the uncertainty of timing of myocardial infarctions in the perioperative setting, review of the other cases suggests a possibility of a relationship with study drug, especially if such an event can occur within the first few doses of parecoxib.*

### **Risk Factors for Clinically Relevant Adverse Events**

A number of risk factors including age (with 65 and 70 years as cut points), gender, BMI, baseline serum creatinine or creatinine clearance, diabetes, CHF, CVD, hypertension, smoking status, time to extubation, use or time on heart pump, pre-operative NSAIDs, pre-operative or concurrent aspirin/salicylate or their interactions were evaluated (data not shown, Table T5.7.3; N93-00-07-816). Comparisons within group and subgroups was by Fisher's exact test, while interactions were compared by Breslow-Day testing were stratified by risk factor.

Within the parecoxib/valdecoxib treatment group, patients with **body mass index (BMI)**  $\geq 30$  kg/m<sup>2</sup> (p=0.014) or with a positive history of **cerebrovascular disease** (p=0.008) were more likely to have a CRAE than patients without a previous cerebrovascular disease or with BMI <30 kg/m<sup>2</sup>. Among placebo patients, those who were **current**

**smokers** were significantly more likely to have a CRAE ( $p=0.011$ ) than were other patients in the placebo group.

When the incidence of CRAEs was analyzed for the interaction of risk factor and treatment group, history of cerebrovascular disease ( $p=0.038$ ) and being a current smoker ( $p=0.007$ ) were identified. History of cardiovascular disease was associated with a higher incidence of CRAEs than was a negative history of cardiovascular disease (52 v. 24%, respectively) for parecoxib/valdecoxib, while the reverse was noted for placebo (0 v. 16%, respectively). Current smokers had a higher incidence of CRAEs than did other patients in the placebo group, while current smokers had a slightly lower incidence of CRAEs than did other patients in the parecoxib/valdecoxib group.

A stepwise logistic regression analysis of potential risk factors revealed within the parecoxib/valdecoxib group, age  $\geq 65$  years (OR: 2.14; CI: 1.11, 4.08), BMI  $\geq 30$  (OR: 1.85; CI: 1.07, 3.21), and prior CVD (OR: 2.95; CI: 1.16, 7.58) were predictive variables associated with risks for CRAE. However, the analysis also suggested that age  $\geq 70$  years was protective (OR: 0.55; CI: 0.22, 1.33). That patients between 65 and 69 years of age are at greater risk of a CRAE, but patients at least 70 years of age are at a reduced risk, suggests some instability of the model.

Other variables associated with an increased risk for CRAEs noted when the analysis involved all patients included history of **diabetes, preoperative aspirin therapy and baseline creatinine  $\geq 106$   $\mu\text{mol/L}$**  (OR: 6.54; CI: 2.03 - 21.11).

#### *Comparative studies for CABG:*

In an attempt to put the results of study 035 into context with respect to current standards of care and outcome, comparative outcome data from two other studies of CABG surgery patients were included in the NDA.

The first of these two studies, EPI 2, is a prospective, international, multicenter, observational study of patients undergoing CABG and/or valve surgery with or without concurrent cardiac or non-cardiac procedures. The study is being conducted by the Ischemia Research and Education Foundation, in conjunction with the Multicenter Study of Perioperative Ischemia, which is a consortium of approximately 300 investigators and 160 academic centers that, since November 1996, have enrolled more than 5,000 patients at 69 centers. The present database was locked at the end of June 2000. This study includes consenting adult patients (between 18 and 75 years, inclusive) undergoing an isolated, primary CABG via median sternotomy with a NYHA Class I - III classification or had a cardiac ejection fraction of at least 35%, and who **had preoperative aspirin treatment** (325 mg/day) maintained throughout the study.

The second source of comparative data is the Society for Thoracic Surgery (STS) database, compiled and maintained by the Society for Thoracic Surgery. Previous published results from this database included patients undergoing a primary, isolated CABG procedure between 1990 and 1994, followed by standard care postoperatively. STS data used for comparison in the present report included results through 1997.

A comparison of the incidences of CRAEs among the three databases is shown in **Table 68**. Since both the EPI 2 and STS databases ended adverse event collection at the time of hospital discharge, the data from study 035 includes only events occurring before hospital discharge. Also, the column of EPI 2 data labeled “Matched Patients” contains only patients who would have satisfied the inclusion/exclusion criteria for Study 035 and were treated at sites included in Study 035. Recognizing the limitations of comparisons between trials, the EPI 2 and STS databases help to add perspective to the data obtained in trial 035.

**Table 68: Comparative Outcome Data from Two Observational Databases<sup>1</sup>**

Adverse Events to Hospital Discharge	Study 035		EPI 2		STS
	Placebo N = 151 n (%)	Parecoxib/ Valdecoxib N = 311 n (%)	Patients Matched to 035 Sites & Entry Criteria N = 547 N (%)**	All Patients N = 3449 n (%)**	All Patients N = 161,018 n (%)
Death	0 (0)	3 (1.0)	3 (0.6)	103 (3.0)	2972 (1.7)‡
MI	0 (0)	1 (0.3)	9 (1.7)	146 (4.2)	1771 (1.1)
CVA accident (+TIA)	1 (0.7)	8 (2.6)	18 (3.2)	245 (7.1)	3703 (2.3)
Deep vein thrombosis	0 (0)	3 (1.0)	0 (0)	4 (0.1)	---
Pulmonary embolism	0 (0)	1 (0.3)	---	---	524 (0.3)
Infection	9 (6.0)	13 (4.2)	81 (15.0)	586 (17.0)	---
Surgical wound infection***	3 (2.0)	7 (2.2)	15 (3)	140 (4)	4214 (2.6)
Renal dysfunction†	6 (4.0)	27 (8.7)	100 (41)	1009 (50)	---
Major renal CRAE††	3 (2.0)	8 (2.6)	4 (0.7)	97 (2.8)	5063 (3.1)
GI event†††	0 (0)	3 (1.0)	4 (0.7)	50 (1.5)	3939 (2.5)

<sup>1</sup> \*\* Percentages calculated based on number of patients with available data for a given event. \*\*\* Surgical wound infection is a subset of all reported infections. ‡ N = 174,806 for death rate in STS. † Includes both renal failure and renal dysfunction in the 035 database. †† Serum creatinine > 2.0 mg/dL and increase of > 0.7 mg/dL from Baseline. ††† Includes bleeds, perforations, and obstructions for study 035, and bleeds for EPI 2 database.

**Adverse Events-Study 035:**

Selected adverse events occurring in study 035 are presented in **Table 69**. The overall incidence of adverse events (over 80%) in each treatment group, likely reflects the population studied and the surgical procedure and post-operative course. The incidence of adverse events was generally similar during the IV dosing period and the entire study period. However, some of these apparent similarities, as well as some of the differences and trends are of interest.

For example, some of the most common adverse events were constipation, nausea and vomiting. The lack of any difference in the placebo versus the “add-on” group of parecoxib/ valdecoxib to this “standard of care”, **suggests that any opioid-sparing effects of these agents is not apparent at a clinical level** i.e. less of the events commonly ascribed to opioids. The results with somnolence, pruritis and respiratory depression would tend to support this lack of an obvious beneficial clinical effect on sparing opioid-related events.

Among other commonly reported **gastrointestinal adverse events** (ulceration, hemorrhage, hemocult positivity SGOT/SGPT increases), the trends suggest more of these events in the parecoxib/valdecoxib group as compared to the placebo group. Of note, post-operative anemia was more common in the parecoxib/valdecoxib group as compared to placebo.

The **cardiovascular and renal events** noted tend to have somewhat mixed results. While there were significantly lower incidences of tachycardia, there were significantly more episodes of supraventricular tachycardia and hypotension in the parecoxib/valdecoxib group; however, this hypotension did not seem to be reflected in episodes of syncope, dizziness or vertigo. On the other hand, events such as hypertension, myocardial infarction, cerebrovascular disorder, hypokalemia, BUN increases, oliguria, and acute renal failure were generally numerically higher in the parecoxib/valdecoxib group.

**Pulmonary events** such as pleural effusion, bronchospasm, pneumonia, and upper respiratory tract infections were significantly less frequent in the parecoxib/valdecoxib group compared to the placebo group; the latter effects did not seem to persist until the end of the study. Episodes of pulmonary embolism or atelectasis did not differ between the treatment groups. Although there were significantly fewer events listed as fever, this did not seem to translate into higher infection rates (data not shown).

Adverse events that increased by at least five percentage points between the IV dosing period and the entire study included peripheral edema, dizziness, constipation, nausea, somnolence, pleural effusion along with fatigue and insomnia (latter two, data not shown).

Most adverse events were mild or moderate in severity (Appendices 4.7.1-4.8.2, N93-00-07-816, data not shown). During the IV dosing period, 10.9% (34/311) and 13.2% (20/151) of patients in the parecoxib/valdecoxib and placebo groups, respectively, had a severe adverse event. During the entire study period, 20.3% (63/311) and 17.2% (26/151) of patients who received parecoxib/valdecoxib and placebo, respectively, experienced a severe adverse event.

**Table 69: Incidence of Selected Adverse Events- Study 035<sup>1,2</sup>**

Event	Placebo (N=151)		Parecoxib/Valdecoxib 40 mg (N=311)	
	IV Dosing Period	Entire Study	IV Dosing Period	Entire Study
Any Event (%)	127 (84.1)	135 (89.4)	251 (80.7)	277 (89.1)
<b>Gastrointestinal</b>				
Duodenal ulcer (perforated)	-	0	-	2 (0.6)
Gastric Ulcer	-	0	-	1 (0.3)
GI hemorrhage	0	0	1 (0.3)	3 (1.0)
Hematemesis	1 (0.7)	1 (0.7)	3 (1.0)	4 (1.3)
Hemocult positivity	0	0	1 (0.3)	2 (0.6)
SGOT increased	2 (1.3)	3 (2.0)	5 (1.6)	11 (3.5)
SGPT increased	0	4 (2.6)	4 (1.3)	12 (3.9)
Constipation	35 (23.2)	56 (37.1)	75 (24.1)	116 (37.3)
Nausea	50 (33.1)	58 (38.4)	116 (37.3)	137 (44.0)
Vomiting	13 (8.6)	17 (11.3)	33 (10.6)	43 (13.8)

Dyspepsia	3 (2.0)	6 (4.0)	9 (2.9)	19 (6.1)
Abdominal Pain	3 (2.0)	5 (3.3)	6 (1.9)	12 (3.9)
<b>Cardiovascular/Renal</b>				
Hypertension-aggravated	1 (0.7)	2 (1.3)	6 (1.9)	7 (2.3)
Hypotension	9 (6.0)	9 (6.0)	37 (11.9)*	39 (12.5)*
Syncope	0	1 (0.7)	3 (1.0)	5 (1.6)
Dizziness	9 (6.0)	27 (17.9)	13 (4.2)	37 (11.9)
Vertigo	-	0	-	1 (0.3)
Edema				
Generalized	6 (4.0)	7 (4.6)	7 (2.3)	9 (2.9)
Peripheral	14 (9.3)	21 (13.9)	35 (11.3)	51 (16.4)
Tachycardia	21 (13.9)	22 (14.6)	15 (4.8)*	22 (7.1)*
Supraventricular tachycardia	0	0	9 (2.9)*	10 (3.2)*
Atrial fibrillation	29 (19.2)	30 (19.9)	43 (13.8)	49 (15.8)
Hypokalemia	5 (3.3)	6 (4.0)	20 (6.4)	22 (7.1)
BUN increased	1 (0.7)	1 (0.7)	8 (2.6)	10 (3.2)
Angina Pectoris	3 (2.0)	3 (2.0)	1 (0.3)	2 (0.6)
Myocardial Infarction	0	1 (0.7)	6 (1.9)	6 (1.9)
Oliguria	15 (9.9)	15 (9.9)	44 (14.1)	45 (14.5)
Acute renal failure	0	0	2 (0.6)	2 (0.6)
Abnormal Renal Function	2 (1.3)	2 (1.3)	7 (2.3)	9 (2.9)
Cerebrovascular Disorder	1 (0.7)	1 (0.7)	6 (1.9)	8 (2.6)
Peripheral Ischemia	1 (0.7)	1 (0.7)	0	0
Thrombophlebitis, deep	0	0	0	2 (0.6)
Pericarditis	0	1 (0.7)	6 (1.9)	7 (2.3)
Hematoma	1 (0.7)	1 (0.7)	1 (0.3)	4 (1.3)
Vasculitis	1 (0.7)	1 (0.7)	0	0
<b>Pulmonary/Post-operative</b>				
Fever	29 (19.2)	32 (21.3)	11 (3.5)*	13 (4.2)*
Pulmonary Embolism	0	0	2 (0.6)	2 (0.6)
Atelectasis	11 (7.3)	14 (9.3)	12 (3.9)	16 (5.1)
Bronchospasm	10 (6.6)	10 (6.6)	5 (1.6)*	6 (1.9)*
Pleural Effusion	18 (11.9)	26 (17.2)	16 (5.1)*	23 (7.4)*
Pneumonia	4 (2.6)	4 (2.6)	1 (0.3)*	4 (1.3)
Respiratory Depression	2 (1.3)	2 (1.3)	6 (1.9)	6 (1.9)
URTI	5 (3.3)	5 (3.3)	0*	3 (1.0)
Post-op incisional pain	5 (3.3)	7 (4.6)	2 (0.6)*	6 (1.9)
Thrombocytopenia	0	0	4 (1.3)	5 (1/6)
Post-op anemia	5 (3.3)	8 (5.3)	22 (7.1)	28 (9.0)
Somnolence	6 (4.0)	19 (12.6)	13 (4.2)	36 (11.6)
Headache	2 (1.3)	2 (1.3)	4 (1.3)	8 (2.6)
Confusion	9 (6.0)	10 (6.6)	13 (4.2)	16 (5.1)
<b>Skin</b>				
Rash	2 (1.3)	4 (2.6)	1 (0.3)	2 (0.6)
Pruritis	3 (2.0)	4 (2.6)	4 (1.3)	6 (1.9)

1 Derived and revised from Table T5.3.1, N93-00-07-816.

2 \* indicates statistically significantly different at  $p < 0.05$ .

### *Incidence of Adverse Events Causing Withdrawal*

The incidences of adverse events causing withdrawal are shown in **Table 70**. During the entire study period, 13.2% of patients in the placebo group and 16.7% of patients in the parecoxib/valdecoxib group withdrew from the study due to an adverse event. Of these, 10.6% and 10.3% of patients in the placebo and parecoxib/valdecoxib treatment groups, respectively, withdrew during the IV dosing period. Statistical comparisons did not reveal any significant differences in the overall or individual event rates between treatment groups.

**Table 70: Incidence of Adverse Events Causing Withdrawal  $\geq 1\%$ - Study 035<sup>1,2</sup>**

Event	Placebo (N=151)		Parecoxib/Valdecoxib 40 mg (N=311)	
	IV Dosing Period	Entire Study	IV Dosing Period	Entire Study
Any Event (%)	16 (10.6)	20 (13.2)	32 (10.3)	52 (16.7)
Gastrointestinal				
Nausea	2.0	2.0	1.6	2.6
Vomiting	1.3	2.0	1.0	1.6
Cardiovascular/Renal				
Hypotension	0	0	0.6	1.0
Cerebrovascular Disorder	0.7	0.7	1.0	1.0
Dizziness	1.3	1.3	0	0.6
BUN increased	0	0	1.0	1.0
Creatinine increased	1.3	1.3	1.9	1.9
Pericarditis	0	0	1.0	1.3
Renal function abnormal	0.7	0.7	1.3	1.3
Pulmonary/Post-operative				
Pneumonia	1.3	1.3	0	0

1 Derived and revised from Table T5.4, N93-00-07-816. Data are expressed as percentage of total.

2 There were no P-values (by Fisher's exact test)  $\leq 0.05$  for any differences between the treatment groups.

**Table 71: Incidence of Extreme Vital Signs- Study 035<sup>1,2</sup>**

Event	Placebo		Parecoxib/Valdecoxib 40 mg	
	IV Dosing Period	PO Dosing Period	IV Dosing Period	PO Dosing Period
Blood pressure (change from baseline)				
Systolic				
15% decrease	27/142 (19.0)	9/97 (9.3)	50/290 (17.2)	16/187 (8.6)
15% increase	29/142 (20.4)	17/97 (17.5)	56/290 (19.3)	29/187 (15.5)
Diastolic				
15% decrease	19/142 (13.4)	11/97 (11.3)	36/290 (12.4)	20/186 (10.8)
15% increase	58/142 (40.8)	23/97 (23.7)	106/290 (36.6)	34/186 (18.3)
Pulse (change from baseline)				
15% decrease	31/142 (21.8)	18/98 (18.4)	95/290 (32.8)*	27/187 (14.4)
15% increase	30/142 (21.1)	12/98 (12.2)	34/290 (11.7)*	25/187 (13.4)
Temperature				
> 39.7 °C	3/142 (2.1)	0/120	4/297 (1.3)	2/245 (0.8)

1 Derived and revised from Table 9j, N93-00-07-816.

2 Data are expressed as number of patients with extreme value/number of patients tested. \* statistically significant from placebo  $P \leq 0.05$ .

### *Serious Adverse Events*

Serious adverse events that occurred in two or more patients in either treatment group during the IV dosing period and the entire study are summarized in **Table 72**. A total of 146 serious adverse events were reported in 74 patients (118 events in 59 patients and 28 events in 15 patients who received parecoxib/valdecoxib or placebo, respectively). These serious events represent 19.0% and 9.9% (entire study) or 6.8% and 6.6% (IV dosing) of patients receiving parecoxib/valdecoxib and placebo, respectively. With the lone exceptions of pneumonia (IV period only) and atrial arrhythmia (entire study), there were as many, but usually more, events in the parecoxib/valdecoxib as compared to the placebo-treated group.

This trend towards more serious adverse events in the parecoxib/valdecoxib group includes gastrointestinal events, thromboembolic and other cardiovascular events, renal events, and infectious episodes.

**Table 72: Incidence of Serious Adverse Events- Study 035<sup>1</sup>**

Event	Placebo (N=151)		Parecoxib/Valdecoxib 40 mg (N=311)	
	IV Dosing Period	Entire Study	IV Dosing Period	Entire Study
Total number of patients (%)	10 (6.6%)	15 (9.9%)	21 (6.8)	59 (19.0)
Total number of events	18	28	39	118
<b>Gastrointestinal</b>				
Duodenal ulcer (perforated)	0	0	0	2
GI hemorrhage	0	0	1	3
Vomiting	0	0	0	2
<b>Cardiovascular/Renal</b>				
Cerebrovascular disorder	1	1	6	9
Thrombophlebitis	0	0	0	3
Hypotension	0	0	1	2
Chest pain (non cardiac)	0	0	2	2
Cardiac failure	1	2	1	3
Atrial arrhythmia	1	2	1	1
Atrial fibrillation	1	1	1	2
Creatinine increase	0	0	1	3
Myocardial infarction	0	1	4	5
Renal function abnormal	0	0	3	3
<b>Pulmonary/Post-operative</b>				
Sternal (deep) wound infection	0	0	0	2
Sternal wound infection	0	0	0	7
Infection (non sternal)	0	0	0	2
Sternal wound drainage	0	0	2	3
Sternal wound dehiscence	0	1	0	2
Sternal instability	0	0	1	2
Bacterial infection	0	0	0	2
Sepsis	0	0	1	2
Post-op anemia	0	0	2	2
Hypoxia	1	1	1	7
Pleural effusion	3	3	1	4
Pneumonia				

<sup>1</sup> Derived and revised from Table T5.5, N93-00-07-816. Data are expressed as number of patients. Only those groups with  $\geq 2$  patients in any treatment group are included.

### *Deaths*

Four deaths occurred among patients receiving the parecoxib/valdecoxib treatment regimen; there were no deaths among the placebo group. Narratives of these deaths can be found in the appendix of this review. A 58-year-old male patient (035-CA0203-0145), who received four doses of IV parecoxib, died on Day 15 (counting first dose day as Day 1) from a duodenal ulcer. A 69-year-old female patient (035-GE0402-1136), who received seven doses of IV parecoxib and thirteen doses of valdecoxib, expired on Day 19 due to a probable myocardial infarction. A 67-year-old male patient (035-UK0303-0938), who received six doses of IV parecoxib and six doses of oral valdecoxib, died on Day 12 from septicemia, sternal wound infection, and bronchopneumonia. A 62-year-old male (035-US0127-0231), who received seven doses of IV parecoxib, expired on Day 6 from massive left cerebellar infarct with brainstem compression (listed as “impression”) and herniation.

### **Summary of Safety Results for Analgesia Study, CABG Surgery Model**

- Most patients (>80%) in either treatment group were exposed for > 7 days.
- The overall incidence of adverse events (over 80%) in each treatment group, likely reflects the population studied and the surgical procedure and post-operative course. The incidence of adverse events was generally similar during the IV dosing period and the entire study period. However, some of these apparent similarities, as well as some of the differences and trends are of interest.
- During the IV dosing period, 10.9% (34/311) and 13.2% (20/151) of patients in the parecoxib/valdecoxib and placebo groups, respectively, had a severe adverse event. During the entire study period, 20.3% (63/311) and 17.2% (26/151) of patients who received parecoxib/valdecoxib and placebo, respectively, experienced a severe adverse event.
- During the IV dosing period, 11.6% of parecoxib /valdecoxib patients and 9.3% of placebo patients had a clinically relevant adverse event; these incidences were comparable to each other. Although not statistically significantly different, the number of deaths, myocardial infarctions, cerebrovascular accidents, pulmonary embolisms, along with renal and pulmonary complications were numerically more frequent for parecoxib during the IV dosing period.
- During the entire study period, 25.7% of parecoxib/valdecoxib patients and 15.2% of placebo patients had a clinically relevant adverse event; this difference was statistically significant. All events, with the exception of myocardial infarctions and major non-GI bleeds, were also numerically more frequent for parecoxib/valdecoxib during the entire study period.
- Differential risk factors for developing clinically relevant adverse events in the parecoxib/valdecoxib group included prior history of cerebrovascular disease and body mass index of  $\geq 30 \text{ kg/m}^2$  and history of cardiovascular disease while current cigarette smoking was a risk factor for placebo patients. For both groups, by logistic regression analysis, history of diabetes, preoperative aspirin therapy and baseline creatinine  $>106 \text{ umol/L}$  also increased risk: the latter was the most predictive risk factor for developing an event.
- Although the adverse event rates in study 035 were within the expected background rates noted in other CABG trials, high-risk patients, such as those identified above may have a higher risk of adverse events with parecoxib/valdecoxib.
- Trends with commonly reported gastrointestinal adverse events (ulceration, hemorrhage, hemoccult positivity SGOT/SGPT increases, post-op anemia) suggest more of these events in the parecoxib/valdecoxib group as compared to the placebo group.
- The cardiovascular and renal events noted tend to have somewhat mixed results. While there were significantly lower incidences of tachycardia, there were statistically significantly more episodes of supraventricular tachycardia and hypotension in the parecoxib/valdecoxib group; however, this hypotension did not seem to be reflected in episodes of syncope, dizziness or vertigo. On the other hand, events such as hypertension, myocardial infarction, cerebrovascular disorder, hypokalemia, BUN increases, oliguria, and acute renal failure were generally numerically higher in the parecoxib/valdecoxib group.

- Pulmonary events such as pleural effusion, bronchospasm, pneumonia, and upper respiratory tract infections were significantly less frequent in the parecoxib/valdecoxib group compared to the placebo group; the latter effects did not seem to persist until the end of the study.
- During the entire study period, 13.2% of patients in the placebo group and 16.7% of patients in the parecoxib/valdecoxib group withdrew from the study due to an adverse event. Of these, 10.6% and 10.3% of patients in the placebo and parecoxib/valdecoxib treatment groups, respectively, withdrew during the IV dosing period.
- Although laboratory data were generally similar between groups, decreases of hemoglobin and/or hematocrit tended to occur more often in the parecoxib/valdecoxib treated groups. Postoperative anemia was higher for patients <65 years than ≥65 years receiving parecoxib/valdecoxib.
- During the IV dosing period, a statistically significantly higher proportion of patients in the parecoxib/valdecoxib group had extreme low pulse than in the placebo group, and a statistically significantly lower proportion of patients in the parecoxib /valdecoxib group than patients in the placebo group had extreme high pulse.
- Serious adverse events occurred in 19.0% and 9.9% (entire study) or 6.8% and 6.6% (IV dosing) of patients receiving parecoxib/valdecoxib and placebo, respectively. With the lone exceptions of pneumonia (IV period only) and atrial arrhythmia (entire study), there were as many, but usually more, events in the parecoxib/valdecoxib as compared to the placebo-treated group. This trend towards more serious adverse events in the parecoxib/valdecoxib group includes gastrointestinal events, thromboembolic and other cardiovascular events, renal events, and infectious episodes.
- Four deaths occurred among patients receiving the parecoxib/valdecoxib treatment regimen; there were no deaths among the placebo group. Causes of death included duodenal ulcer, probable myocardial infarction, septicemia, and cerebellar infarct with brainstem compression and herniation.
- Any opioid-sparing effects by the addition of parecoxib/valdecoxib is not apparent by comparing the pattern of adverse events (i.e. constipation, nausea, vomiting, somnolence, pruritis, respiratory depression) to the standard of care/placebo group. Events commonly ascribed to opioids tended to be more, not less, common in the parecoxib/valdecoxib group.

### **Renal Effects:**

Mechanism-based (i.e., based on COX-2 inhibition) disturbance of renal function was observed in rat and dog models of volume-contraction. In **animal models** based on an activated renin-angiotensin axis, valdecoxib **decreased renal blood flow**, as well as the **rates of glomerular filtration** and urine formation, **and the urinary excretion of prostanoids**. These effects occurred **at plasma concentrations of valdecoxib that are within its window of COX-2-selective action**. These results suggest that caution should be exercised if parecoxib or valdecoxib is used clinically in patients with high renin states (e.g., volume depletion, congestive heart failure).

Reviewer's comment: Readers interested in more detailed analysis of the renal effects of parecoxib/valdecoxib should read the review of Dr. Douglas Throckmorton.

### **Placebo-Controlled Multiple Dose Studies vs. Ketorolac:**

During the platelet studies in healthy volunteers (studies 015, 017, and 027) discussed earlier, certain renal parameters were measured (as secondary variables). These parameters included urinary excretion rates for **11-dehydro-TxB<sub>2</sub>** (derived partly from platelets), prostaglandin excretion (**PGE<sub>2</sub> and 6-keto-PGF<sub>1α</sub>**; number of methodologic as well as biologic variables can affect urinary prostaglandin measurements in humans) and **fractional sodium excretion**. No statistical analyses were conducted for the prostaglandin data, as the studies were not powered to detect differences between treatment groups.

Treatment with parecoxib (up to 40 mg BID) resulted in small numerical changes in median values of urinary 11-dehydro- TxB<sub>2</sub> excretion (studies 015 and 017, day 1 or 8) while ketorolac 15 or 30 mg QID reduced it to approximately half the baseline rate (day 1 and 5). Treatment with parecoxib (10 or 40 mg BID) tended to reduce urinary PGE<sub>2</sub> excretion but the effect was of lower magnitude than that observed after treatment with ketorolac 15 or 30 mg BID. Treatment with parecoxib (10- 40 mg BID) reduced urinary 6-keto- PGF<sub>1α</sub> excretion on both the first and final dose days, but the effects were not as great as was observed for treatment with ketorolac 15 or 30 mg QID. Fractional sodium excretion was transiently reduced by statistically significant margins on the first day of treatment with parecoxib (10-40 mg BID). Reductions of 0.220% to 0.270% in parecoxib groups, compared to reductions of no more than 0.091% with placebo. These reductions were significantly less severe than those observed for ketorolac 15 or 30 mg QID (mean reductions of 0.360% to 0.568%). In all cases, fractional sodium excretion rates returned to normal (not significantly different from baseline) by the last dose day.

***Reviewer's comment: These findings support the conclusion that COX-2 influences renal function.***

### **Adverse Events Related to Renal Function:**

Adverse events, potentially related to renal function, were consolidated as "renal adverse events" for review; this included urinary system disorders of the W.H.O.a.r.t. body system classifications as well as adverse events from other body systems (e.g., edema, hypertension). The results (Tables T11.1.1, Tables 4.5.2 –4, Tables T8.3.1-2, Tables T7.3.1-2, T11.2.1, Table T11.4.2, Table T11.5.2; N93-00-07-816) are summarized as follows:

- In the general surgery trials, there were few renal adverse events in any treatment group (2.4% was the highest incidence rate; peripheral edema with NSAIDs). The most common renal adverse events were **hypertension and peripheral edema**. There was no obvious pattern of increased incidence across treatments. None of the renal adverse event rates were statistically significantly different between treatment groups.
- In the pharmacological differentiation studies (011, 015, 016, 017, 026, 027 and 030) with healthy young or elderly subjects, there was a dose-dependent increase in the **incidence of peripheral edema associated with parecoxib** (parecoxib 20 mg BID

1.8%, parecoxib 40 mg BID 3.9%). The combined incidence for parecoxib (3.1%) was statistically significantly higher than for placebo (p=0.023) but not NSAIDs (0.9%). These episodes of edema occurred in both young and elderly subjects. Two subjects receiving parecoxib 20 mg BID (both in Study 017) had simultaneous adverse events consisting of creatinine, BUN, and weight increases, consistent with transient renal insufficiency; these patients had no prior histories of edema.

- Renal adverse events in the valdecoxib (highest dose only 20 mg QD) longer-term safety study occurred at a generally low rate (highest incidence of 3.4% for peripheral edema, valdecoxib 10 mg) and did not suggest any obvious dose-dependent increase. The incidences of the most common renal adverse events, hypertension, peripheral edema, BUN and creatinine increases, were not statistically significantly different between treatment groups.
- Among CABG surgery patients with a **history of diabetes mellitus**, the risk difference (RD) for **peripheral edema** was 19.7 (higher risk for patients receiving parecoxib or valdecoxib than for patients receiving placebo). The RD for patients without a history of diabetes was -1.9 (slightly higher risk for patients receiving placebo). The difference in these RDs (21.7) was statistically significant (p=0.008). In patients with a history of **hypertension**, the RD for **oliguria** was 0.7 (slightly higher risk for patients receiving parecoxib/valdecoxib than for patients receiving placebo). The RD for patients without a history of hypertension was 16.9 (higher risk for patients receiving parecoxib or valdecoxib). The difference in these RDs (-16.2) was statistically significant (p=0.018).

In the **CABG surgery trial**, where patients were treated for longer periods of time, renal adverse events were more common than in the general surgery trials (**Table 83**). The most commonly reported adverse events were **peripheral edema and oliguria**. Although there were no statistically significant differences between the two groups, **trends** suggested more events for parecoxib/valdecoxib compared to placebo-treated patients.

**Table 83: Renal Adverse Events ≥1% -CABG Surgery Trial<sup>1</sup>**

<u>Event</u>	<b>Placebo</b> (N=151)		<b>Parecoxib/Valdecoxib 40 mg</b> (N=311)	
	IV Dosing Period	Entire Study	IV Dosing Period	Entire Study
BUN increased	0.7	0.7	2.6	3.2
Creatinine increased	4.0	4.0	3.9	5.8
Edema generalized	4.0	4.6	2.3	2.9
Edema peripheral	9.3	13.9	11.3	16.4
Hyperkalemia	0.7	0.7	1.0	1.6
Hypertension	0	0	1.3	1.3
Hypertension aggravated	0.7	1.3	1.9	2.3
Oliguria	9.9	9.9	14.1	14.5
Renal function abnormal	1.3	1.3	2.3	2.9

<sup>1</sup> Derived from Table T11.1.2, N93-00-07-816. Data represent percentages of patients.

#### Serious and Clinically Relevant Adverse Events Related to Renal Function:

Of the 17 serious renal adverse events noted in this NDA, 14 occurred in patients who received any dose of parecoxib or valdecoxib. The majority of the cases (11 of the 14 cases) were from the CABG surgery trial and most (10 of the 14 cases) did not result in withdrawal from study participation. Reasons included aggravated hypertension (3 cases), peripheral edema (1 case), fluid overload (1 case), urinary retention or infection (2 cases), acute renal failure (1 case), abnormal renal function (3 cases) and increases of creatinine (3 cases). Although the events from the CABG trial (which included all three cases of creatinine increases) are multifactorial in etiology, it was felt that patient US0131-0273 (a 61-year-old man who developed oliguria and hypotension with a systolic pressure 59 mm/Hg on the first treatment day following CABG surgery), was attributable to parecoxib.

*Reviewer's comment: Although difficult to interpret without other treatment arms, it is of interest to note that most of the serious renal events, in a patient population likely to receive it, occurred with parecoxib/valdecoxib vs. placebo.*

As noted earlier, clinically relevant adverse renal events were adjudicated by an outside committee (CRAEC). For changes in BUN and creatinine, a separate set of criteria deemed to be more appropriate for CABG surgery patients defined major clinically relevant renal adverse events as those events associated with a serum creatinine value > 2.0 mg/dL and an increase of > 0.7 mg/dL from baseline. Using these criteria, 8 (2.6%) parecoxib/valdecoxib and 4 (2.6%) placebo patients had major renal events in study 035. Of these major renal events, 7 were detected by laboratory tests and required no treatment, and 3 were first noted as oliguria. Seven of these events resulted in discontinuation of study medication. All but 1 **patient** (035-CA0203-0145, who **died** of respiratory arrest **eight days after oliguria onset**; see Appendix: Narrative of Deaths: Parecoxib Trials) recovered from these events.

In the valdecoxib longer-term OA trial, the CRAEC adjudicated renal events for 33 patients as being clinically significant: 1 (0.5%) in the placebo group; 6 (2.9%) in the valdecoxib 10 mg QD dose group; 4 (1.8%) in the valdecoxib 20 mg QD dose group; 14 (6.8%) in the ibuprofen 800 mg TID dose group; and 8 (3.8%) in the diclofenac sodium 75 mg BID dose group. Of the 33 patients with clinically significant renal events, two patients were withdrawn due to treatment-emergent adverse events.

#### **Cardiovascular Effects:**

In the nonclinical cardiovascular safety studies, oral valdecoxib and IV parecoxib did not appear to have significant effects on arterial pressure, heart rate or hemodynamics. In conscious dogs, detailed study of the ECG intervals including the QT intervals, gave normal results.

#### **Conduction Abnormalities, Arrhythmias and ECG Findings**

Twelve-lead electrocardiograms (ECGs) were performed at pre- and post-treatment visits in five phase I/II studies (001, 002, 008, 009, and 012); ECGs were normal for all but 20 of 188 (10.6%) subjects; the exceptions were not considered to be clinically significant. An in-depth analysis of the QT interval was conducted in subjects (study 91-056) who received a single 20 mg dose of valdecoxib on Days 1, 8, 15 and 22; this study was designed as a bioequivalence study to compare two valdecoxib tablet formulations (Phase III versus commercial). Subjects underwent 12-lead ECG assessments on each dosing day at predose and approximately 3 and 24 hours postdose. On each of the individual dosing days, none of the mean predose or postdose QT intervals were >400 msec, and the changes in mean postdose QT intervals were  $\leq 5\%$  of the predose values. QT intervals, corrected for heart rate (QTc) using Bazett's methodology, mean QTc intervals were not prolonged following valdecoxib administration (mean decreases of  $\leq 4\%$  [-15.8 msec] from predose were observed in both formulation groups). Eight subjects (7 males, 1 female) had postdose QT or QTc intervals > 430 msec or postdose increases in QT or QTc > 30 msec. The majority of these events were single, transient occurrences; one of these individual changes in QT or QTc were considered clinically meaningful.

***Reviewer's comment: Although the Sponsor noted that a single dose of valdecoxib 20 mg did not have a clinically significant effect on QT or QTc intervals (or on any of the remaining ECG parameters), further study with more clinically relevant doses and in patients would be more appropriate to answer these questions.***

The incidences of heart rate and rhythm disorders reported as adverse events or withdrawals in the **general surgery trials** (Table T4.5.1 and Table 15.c, N93-00-07-816) suggested no significant treatment-related effects associated with the use of parecoxib.

The results for the **CABG trial** are noted in **Table 84**. Here, there was a higher incidence of atrial fibrillation and significantly more episodes of tachycardia in placebo-treated patients while ventricular arrhythmia and a significantly higher incidence of supraventricular tachycardia were noted in patients treated with parecoxib/valdecoxib compared to patients treated with placebo. Patients were withdrawn from the CABG surgery study as a result of cardiac conduction abnormalities or arrhythmias. Five patients (1.6%) receiving parecoxib/valdecoxib experienced a serious adverse event related to heart or rhythm disorders as compared to four (2.6%) placebo-treated patients; parecoxib did not seem associated with any particular type of arrhythmia or conduction disturbance. Subgroup analyses in the CABG study by age, history of hypertension, cardiovascular atherosclerotic disease and cerebrovascular disease did not reveal a significant risk difference for heart rate or rhythm-related adverse events (Tables T5.6.1-2, T21.2.1-2, T23.2.2, T23.4.2, and T23.6.2; N93-00-07-816).

**Table 84: Heart Rate and Rhythm Disorders, CABG Surgery Study<sup>1</sup>**

Event	IV Dosing Period		Entire Study	
	Placebo (N=151)	Parecoxib (N=311)	Placebo (N=151)	Parecoxib/ Valdecoxib (N=311)
Arrhythmia	2.0	2.3	4.0	2.6
Arrhythmia atrial	2.0	1.0	3.3	1.0
Arrhythmia nodal	0.7	0	0.7	0
Arrhythmia ventricular	0.7	2.6	1.3	2.6
AV block	0.7	0.3	0.7	0.3
Bradycardia	0.7	1.9	2.0	1.9
Bundle branch block	0	0	0	0.3
Extrasystoles	0	1.0	0	1.0
Fibrillation atrial	19.2	13.8	19.9	15.8
Palpitation	1.3	1.6	1.3	1.6
Tachycardia	13.9	4.8	14.6	7.1
Tachycardia supraventricular	0	2.9	0	3.2
Tachycardia ventricular	1.3	0.6	2.0	1.0

<sup>1</sup> Derived from Table T5.3.1, N93-00-07-816. Numbers represent percentages. By Fischer's exact test, the following were significantly different: tachycardia (P=0.001 and 0.017, IV and oral, respectively), supraventricular tachycardia (p=0.034 and 0.035, IV and oral, respectively).

#### Vaso-Occlusive Adverse Events:

In the **general surgery trials**, no treatment-related differences were apparent to suggest that parecoxib was associated with an increased incidence of vaso-occlusive adverse events in patients participating in the general surgery studies. One patient (0.3%) treated with parecoxib 20 mg and two patients (1.2%) treated with NSAIDs experienced myocardial infarctions. Two patients, one (0.3%) receiving parecoxib 20 mg and one (0.3%) receiving a dose of 40 mg experienced a cerebrovascular disorder; 2 NSAID-treated patients (1.2%) experienced a cerebrovascular disorder. One placebo-treated patient was withdrawn from the general surgery studies due to peripheral ischemia (Table T4.7.1, N93-00-07-816).

In the **CABG trial** (see separate review of this trial), although there were no statistically significant differences detected between the treatment groups with regards to adverse events, there were higher incidences rate of **myocardial infarctions** (1.9% vs 0.7%) and **cerebrovascular disorders** (2.6% vs 0.7%) in patients receiving parecoxib/valdecoxib when compared to placebo-treated patients. Myocardial infarction or cerebrovascular disorders led to withdrawal of two patients treated with placebo and three patients who received parecoxib/valdecoxib. Subgroup analyses of adverse events dichotomized by age (<65 years and >65 years) did not show a statistically significant excess of myocardial vaso-occlusive adverse events (myocardial infarction, myocardial ischemia or angina pectoris) with parecoxib/valdecoxib treatment in elderly patients participating in the CABG surgery trial (Table T5.6.1, N93-00-07-816).

Reviewer's comment: No myocardial infarctions were observed in the valdecoxib OA study in any treatment group and no cerebrovascular disorders were noted in the valdecoxib-treated patients.

**Serious vaso-occlusive adverse events** that occurred in any study included in this NDA are summarized in **Table 85**. In the **general surgery** trials, 4 serious adverse events (3 cases of pulmonary embolism, 1 thrombophlebitis deep) occurred in morphine-treated patients; four events (2 myocardial infarctions, 2 cerebrovascular disorders) in ketorolac-treated patients; and 6 events (3 cases of thrombophlebitis deep, 1 myocardial infarction and 2 cerebrovascular disorders) in parecoxib-treated patients.

*Reviewer's comment: Most of the exposure to parecoxib or valdecoxib in these general surgery trials was single dose.*

In the **CABG surgery** study, 9 patients (2.9%) experienced cerebrovascular disorders, 5 patients (1.6%) experienced myocardial infarctions, 3 patients (1.0%) experienced thrombophlebitis deep, and 1 patient (0.3%) experienced urgent revascularization in the parecoxib/valdecoxib-treated group. This compares with 2 similar events in the placebo-treated patients: 1 patient (0.7%) with myocardial infarction and 1 patient (0.7%) with cerebrovascular disorder.

**Table 85: Serious Adverse Events Related to Vaso-Occlusive Events<sup>1</sup>**

Event	Study	Treatment (number of events)
Thrombophlebitis, deep	018	Parecoxib (3) Morphine (1)
	020	Parecoxib (1)
	035	Valdecoxib (3)*
Cerebrovascular disorder	018	Ketorolac (1)
	020	Ketorolac (1) Parecoxib (1)
	035	Parecoxib (6) Valdecoxib (3) Placebo (1)
	037	Parecoxib (1)
Pulmonary embolism	018	Morphine (1)
	019	Morphine (1)
	020	Morphine (1)
	035	Valdecoxib (1)* Parecoxib (1)
Myocardial infarction	018	Ketorolac (1)
	020	Ketorolac (1)
	035	Parecoxib (4) Valdecoxib (1) Placebo (1)
	037	Parecoxib (1)
Angina pectoris	035	Placebo (1)
	91-048	Ibuprofen (1)
Urgent revascularization	035	Valdecoxib (1)
Cardiac tamponade	035	Valdecoxib (1)
Pericardial effusion	035	Valdecoxib (1)
Coronary artery disorder	91-048	Diclofenac (2)

Hemopericardium	91-048	Ibuprofen (1)
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1 Derived from Appendix 2.1.1 and Appendix 2.2; N93-00-07-816. Valdecoxib is 10 or 20 mg. Parecoxib is 20 or 40 mg. There was one patient (\*) who had both a pulmonary embolism and DVT.

***Reviewer’s comment: It is of interest to note that in the CABG study (035), 21 of the 23 patients listed having serious “vaso-occlusive” events had received either parecoxib or valdecoxib. If a composite endpoint of MI, CVA, PE and DVT were created, 18 of 311 patients (5.5%) versus 3 of 151 patients (2.0%) would be included in the parecoxib/valdecoxib and placebo groups, respectively. Of the cerebrovascular disorders, all events appeared to be related to ischemia or embolism; only one case in the parecoxib group appears to have had a hemorrhagic component to it. Eleven of the patients in the parecoxib/valdecoxib group were ≥ 65 years, nine of these having cerebrovascular events.***

### **Hemodynamic Adverse Events and Blood Pressure:**

In the **general surgery trials**, no significant differences in these adverse events were seen between parecoxib and the NSAID groups, however, a significantly higher incidence of supine systolic and diastolic blood pressure reductions greater than 15% was observed for the parecoxib than the placebo group. Small, albeit significant, mean reductions in supine systolic blood pressure were also evident for parecoxib when compared to placebo over the first 4 hours after treatment (Table 4.19.1 and T4.22.2, N93-00-07-816).

In the **CABG surgery** study, there were statistically significantly higher incidences of **hypotension** during both the IV dosing period and the entire study period for patients receiving parecoxib/valdecoxib, compared to patients receiving placebo. Subgroup analyses by history of hypertension showed a statistically significant risk difference for the event of hypotension. There were no statistically significant differences in the other events of hypertension or cardiac failure.

There were few events of serious adverse events of hypertension, hypotension, and cardiac failure in the general surgery studies. In the CABG surgery study, there were two events that the Investigator attribution as “uncertain” while 4 events were not attributed to either parecoxib or valdecoxib (Appendix 2.1.1 and 2.2; N93-00-07-816).

#### *“Risk-Benefit” analysis of Parecoxib:*

Any type of risk or benefit needs to be talked about in context. In this NDA, there would seem to be several levels for such discussion. This section will attempt to look at both the big picture, as well as its key components. This particular discussion is complicated by the fact that parecoxib in an “inactive” parenteral prodrug of an orally “active” agent valdecoxib, which is the subject of another concurrent NDA review. Therefore, lines are “fuzzy” in terms of where the efficacy associated with parecoxib ends and that of valdecoxib begins; the same is true for issues surrounding safety. Also complicating this discussion are the multiple claims for efficacy that the Sponsor is seeking which include not only the “usual” treatment of established pain, but also prevention or preemptive treatment of pain as well as language in the label as to how parecoxib has an “opioid-sparing” effect.

The overriding (and arguably most conservative) principle for what follows is that the efficacy associated with parecoxib derives solely from the trials in which it had an important role whereas the safety associated with parecoxib is better appreciated by including data also involving the use of valdecoxib. The limiting aspect of most NDA applications is a robust assessment of the safety of the compound of interest; parecoxib appears to be no exception.

Of the 36 trials noted in this NDA, nine were considered “pivotal” and one was considered “supportive” toward the proposed labeling claims. The nine pivotal trials included studies 014 and 025 (oral surgery), 018 and 020 (post-orthopedic surgery), 019 and 021 (post-gynecologic surgery), 022 and 037 (pre-operative surgery) and the CABG trial 035 (opioid-sparing). The supportive trial was 029, this also evaluated opioid-sparing in a post-gynecologic surgical setting. Most of the experience (approximately 64%) with parecoxib, in terms of both efficacy and safety, derives from single-dose experiences (Table 65). This single-dose exposure includes all the studies listed above with the exception of 020, 021 (limited multiple dose component, discussed below), study 029 (included 3 doses) and study 035; the latter being the most robust assessment of the safety of parecoxib in a surgical setting.

Safety discussion:

**Consideration of “safety” in a post-surgical setting, particularly as included in this NDA, is difficult for a variety of reasons. For example, patients enrolled in oral surgery trials do not have the same risk factors such as age, co-morbidities or medications as those enrolled in a CABG trial. Even when patients can be balanced for risk factors in any individual trial, surgical manipulations in a hip or knee replacement procedure, abdominal hysterectomy and CABG settings undoubtedly do not uniformly impact important parameters that factor into an assessment of safety such as pain pathways, cytokines and proinflammatory mediator release, or the development of a risk such as a hypercoagulable state. Therefore, the intrinsic heterogeneity of surgical procedures and patients makes adequate risk assessment difficult in a “controlled” surgical setting where patients are screened for predefined inclusion and exclusion criteria. An even more difficult “extrapolation” of the relative safety of parecoxib in this NDA would be to subjects (or patients) who then become patients due to some type of trauma or emergency. This “all comers” approach to safety in people at all levels of risk is a special area of concern for a compound such as parecoxib. Acute clinical situations such as these often engender an abnormal or unstable cardiovascular status confounded by numerous factors (fluid imbalances, increased catecholamine secretion, etc.) whose impact may not be adequately addressed by the types of trials included in this NDA.**

**Yet another layer of complication is the fact that data on the safety of single doses of parecoxib can not predict that of a multiple dose experience. Consequently, much of the safety data noted in this NDA will underestimate the true risk. However, the most robust data on the safety of parecoxib in terms of dose and duration of use came from the CABG trial. For this section, therefore, the safety profile of parecoxib in the CABG trial will be discussed separately from the other surgical studies.**

#### Overall safety (excludes CABG)

The safety results from the **general surgery trials** of patients who were treated briefly (most single dose) either postoperatively or preoperatively with one or more doses (20 to 40 mg) of parecoxib need to be interpreted with caution. By comparison to results with placebo, the major **safety concerns may relate more to the surgery and associated medical management care than the treatments evaluated** (i.e. parecoxib, morphine,

ketorolac). There are **suggestions of trends that parecoxib is associated with more hypotensive episodes, lower blood pressures, and more anemia** than the other treatment groups. However, the frequency and character of severe or serious adverse events does not suggest these trends are clinically important. The adverse events most frequently observed with parecoxib were headache, fever, nausea, vomiting, and pruritus; however, the incidences of these complaints in placebo-treated patients were generally similar. No obvious unusual laboratory findings or vital sign changes were seen with parecoxib administration.

Similarly, the incidence and pattern of adverse events in patients undergoing **dental extraction** likely represent effects of surgery and anesthesia rather than the effects of treatment with parecoxib or the comparators (Tramadol may be the exception). Across all treatment groups, the most common types of adverse events were nausea, dizziness, headache, vomiting, and injection site ecchymosis. The incidences of nausea and vomiting associated with parecoxib were lower than those associated with NSAIDs or placebo. No specific adverse event was observed significantly more frequently with parecoxib than with either placebo or NSAIDs. In these studies, **there were no obvious dose-related increases in adverse events associated with parecoxib.**

The short-term, **pharmacological, pharmacokinetic and drug interaction trials** provided early information on the safety of parecoxib administered to mostly healthy (exception of study 012 in patients with hepatic impairment) young and elderly people (over 100 subjects received parecoxib 40 mg BID). In this setting, parecoxib appeared to be generally well tolerated. Adverse events consisted of those not unexpected in these types of trials (dizziness, headache, nausea) although there were **suggestions that peripheral edema, increases of ALT and AST, and changes in blood pressure may be areas of concern.** No consistent pattern in the incidence of specific adverse events was apparent in these studies. There were no deaths or serious adverse events in this study and only a few withdrawals (urticaria and weight increase).

**Exposure to valdecoxib 10 or 20 mg** for up to 12 weeks in OA patients did not result in the emergence of any obviously clinically important adverse events when compared to the other treatments; it appeared to be generally safe and well tolerated. However, it is **difficult to extrapolate these results**, obtained in patients who are generally healthy to patients undergoing a surgical procedure; the same limitation would seem to apply to the doses since higher doses would generally be required in the latter situations. Nonetheless, the results observed for events such as rashes, bronchospasm, GI events, liver function tests, effects of formed blood elements, and renal function do not suggest important concerns at these doses. No meaningful age, gender, racial, or demographic interactions were apparent. Also, no drug interactions were apparent.

**There were only two deaths in all these trials**, one in the general surgery studies (single dose of parecoxib with death nine days later) and the other in the OA study (patient received ibuprofen).

### **Coronary Artery Bypass Graft (CABG) trial:**

Although this trial was the most robust test of the overall safety of parecoxib, it could be argued that even here the safety results in these “healthy CABG” patients may have underestimated the true risk that may occur with more widespread use of parecoxib. Examples of this oxymoron may well include most of the exclusion criteria before the surgery (like emergency CABG, occurrence of MI within 48 hours, CVA or TIA within 6 months, etc.) as well as many of the criteria for inclusion before surgery or those applied to the intra- or postoperative period (see description of CABG trial earlier in this review).

In addition to the fact that this is a single trial, it also lacks any positive control for comparison of safety (or efficacy). In the postsurgical setting, where patients may be unable to tolerate oral medications, the only parenteral comparator NSAID available for use in the United States is ketorolac tromethamine (**Toradol®**). Owing to concerns about the high rate of serious GI complications and other adverse effects, ketorolac has been withdrawn from some markets (France and Germany) while its use is limited in others (U.S.-5 continuous days; U.K -2 days). Lacking data even in the “controlled” situation of this clinical trial, **no valid comparisons are possible between parecoxib and ketorolac**, only to the “placebo” standard of care. Unfortunately, therefore, no useful extrapolations of safety comparisons can be made between these same two compounds in any other surgical or emergency situation.

**The adverse event profile of parecoxib was generally worse than that of placebo** in this trial. For example, looking at the overall incidence of adverse events (over 80%) in the two treatment groups, while many likely reflect the surgical procedure and intra- and post-operative course, some trends seemed to emerge such as **more severe adverse events associated with parecoxib /valdecoxib over the course of the study**. During the IV dosing period, there were numerically more parecoxib /valdecoxib patients with “clinically relevant” adverse events. Although not statistically significantly different, the number of deaths, myocardial infarctions, cerebrovascular accidents, pulmonary embolisms, along with renal and pulmonary complications were also numerically more frequent for parecoxib during this IV dosing period than placebo. In fact, **during the entire study period, the incidence of these “clinically relevant” adverse events associated with parecoxib/valdecoxib was statistically significantly different than placebo**. Once again, although individual events were not significantly different between the two groups, with few exceptions adverse events were numerically more frequent for parecoxib/valdecoxib than placebo. Similarly, during the entire study period, more patients in the parecoxib/valdecoxib versus the placebo group withdrew from the study due to an adverse event. And perhaps most importantly of all, since the causes were similar in nature to what was noted with the adverse events (i.e. duodenal ulcer, myocardial infarction, infectious complications, cerebrovascular accident), **all four deaths occurred among patients receiving the parecoxib/valdecoxib treatment regimen; there were no deaths among the placebo group**.

The Sponsor has argued that certain high-risk patients, such as those with a prior history of cerebrovascular disease or a body mass index of  $\geq 30 \text{ kg/m}^2$  or elevated baseline creatinine levels, may have a higher risk of adverse events with parecoxib/valdecoxib.

The implication may be that such patients can be identified prospectively and hence avoided or managed differently. It is noteworthy that the vast majority of patients enrolled in this trial were on aspirin to prevent myocardial infarctions and other thromboembolic-type phenomenon. Regarding myocardial infarctions, the incidence of these types of events was different between events adjudicated and considered “clinically relevant” compared to those listed as serious adverse events. It is of interest that one of the events for parecoxib listed as not being clinically relevant by the committee resulted in the death of that patient from a myocardial infarction. Nonetheless, taken as a composite type endpoint to include events such myocardial infarctions, cerebrovascular accidents, deep venous thrombosis and pulmonary embolism (Table 67 or 69, for example), there were consistently more of these types of thromboembolic outcomes in the parecoxib/valdecoxib versus the placebo groups. **If it is true that certain adverse events, even when prophylaxed against (in this case aspirin) still can occur in short-term, perioperative settings, then it is even more worrisome to consider what the pattern and frequency of adverse events may be in situations where risks are not addressed or can not be altered.**

It is also worrisome to consider the breath of organ systems adversely impacted by parecoxib and valdecoxib compared to the standard of care in this trial. For example, GI events such as duodenal or gastric ulcer or hemorrhage or hemocult positivity only occurred in patients receiving parecoxib/valdecoxib. Similarly, sternal wound infections, drainage and dehiscence were also only noted in the parecoxib/valdecoxib group. Some of the events, such as hypotension, were not only unique to parecoxib but were also statistically significantly different than placebo. Furthermore, increases of SGOT or SGOT, supraventricular tachycardia, hypokalemia, increases of BUN, acute renal failure, oliguria, hematoma, thrombocytopenia and post-operative anemia were also numerically more frequent with parecoxib/valdecoxib as compared to placebo. Whether these trends can be ascribed only to drug and/or mechanism-related causes, or also reflect some other more technical aspect of this trial such as the unequal randomization in this trial, remain elusive.

While it may be true that certain adverse events, such as atelectasis, pleural effusion and pneumonia were more common in the placebo group in this trial, these results do not support any conclusion that parecoxib/valdecoxib had significant opioid sparing qualities. If adverse events typically associated with opioids include outcomes such as constipation, nausea, vomiting, somnolence, pruritis and respiratory depression (Table 69), these events were no less common in the parecoxib/valdecoxib groups than the standard of care groups; in fact, these events were often more common. Further study of prospectively defined endpoints, such as time to discharge from intensive care units or from the hospital may be necessary to fully appreciate the clinical importance of any numeric or statistically significant differences in opioid use.

#### **Safety conclusions:**

Most of the data on the safety of parecoxib, and its metabolite valdecoxib, in this NDA resulted from single dose, or limited multiple dose administration. In these surgical settings with such limited exposure, it is not possible to adequately address the necessary

conclusions regarding the overall safety profile of parecoxib. To conclude from such limited experience that parecoxib “was generally well tolerated” could be argued to be a requirement for further, more in depth study of this or any other drug; this is particularly true for any drug contending to have an improved safety profile over extant therapies.

Without robust head-to-head comparisons with currently available therapies, useful inferences are impossible. In the CABG trial, the comparisons that can be made to the standard of care/placebo group note trends, and in some cases, statistically significant differences to suggest that parecoxib has consistent and important adverse events associated with its use. That these differences appear evident in the population studied, for the durations studied and in the face of certain compounds meant to prevent their occurrence brings substantial concern to the overall safety of parecoxib. Further study will be important to add to an understanding of the true safety liability of this potentially important new analgesic.

If it is argued that the dose (40 mg BID) of parecoxib (and valdecoxib) used in the CABG trial is too high, and this high dose contributed to a less favorable safety profile for parecoxib, then the lack of data on the safety of multiple doses of parecoxib in any acute or surgical setting becomes more important owing to the observation that doses of parecoxib lower than 40 mg did not seem to consistently demonstrate efficacy in trials included in this NDA. If parecoxib has both a narrow efficacy and safety window, this emphasizes the importance of continued study to adequately define these windows.

### **Overall Conclusions:**

- Parecoxib sodium, at single doses of 40 mg, is consistently efficacious (with respect to onset, magnitude, and duration of analgesia) in the management of acute pain; 20 mg is not consistently efficacious as a single-dose analgesic.
- Multiple dose data with parecoxib sodium are limited and do not allow for characterization of the safe and effective dose, or dosing interval after the first dose.
- IV and IM parecoxib sodium appear to provide comparable analgesic efficacy when administered at the same dose although most of the data in this NDA derives from IV.
- Parecoxib sodium did not consistently reduce opioid consumption.
- The safety of parecoxib sodium has not been adequately addressed. Most (approximately two thirds) of the data on safety and efficacy in the original NDA was obtained from patients or subjects exposed to single doses of parecoxib sodium. While such data is fundamental to supporting the efficacy and safety of parecoxib sodium, it is insufficient to fully characterize the safety and efficacy of this compound.

- Safety data from the CABG trial suggest that certain subgroups of patients may be at increased risks for serious adverse events. Furthermore, these data can not exclude the possibility of an important safety liability associated with parecoxib sodium, particularly with repeated doses, over placebo.
- The proposed labeling claims for management of postoperative pain or for the preemptive treatment of pain or for opioid sparing with parecoxib sodium are not supported by the data available in this NDA either due to insufficient data or lack of replication of results.

*Regulatory discussion*

Parecoxib represents the first “COX-2 selective” agent to be submitted for parenteral use as an analgesic. The Sponsor has proposed labeling which includes the following:

**“Xaptek is indicated for the prevention and treatment of moderate to severe pain in adults. In addition, for surgical pain requiring analgesia at the opioid level, Xaptek significantly reduces opioid consumption. “**

Data from the clinical trials included in this NDA are inadequate to support any of the claims including treatment, prevention of pain or opioid sparing either due to insufficient data or to lack of replication of results. Furthermore, data on the safety of parecoxib suggest that it has important clinical differences from placebo that need to be studied in more detail, and in a variety of other settings, to help understand whether the efficacy benefits are overshadowed by safety risks. Consequently, with reference to 21 CFR 314.125 (b) (4) (5), it is recommended that the data in this NDA support the conclusion that parecoxib is not approvable.