## Renal Safety:

***Reviewer's comment: For a detailed examination of the results of Cx on renal function and safety, the interested reader is encouraged to read the cardiorenal consult.***

Experimental and clinical evidence demonstrates that NSAIDs reduce renal function when renal perfusion is dependent on prostaglandin formation. Patients at risk for acute ischemic renal failure (renal decompensation) include those with a variety of renal diseases, congestive heart failure, cirrhosis with ascites, volume depletion and diuretic use. These effects are normally readily reversible upon withdrawal of the drug. NSAIDs can also produce fluid retention leading to edema formation, interfere with the blood pressure-lowering effects of certain antihypertensive medication and rarely lead to chronic renal injury such as interstitial nephritis or papillary necrosis.

Cyclooxygenase activity can be found throughout the kidney although enzyme activity is most abundantly expressed in four discrete sites; the glomerular afferent and efferent arterioles, the glomerulus, the interstitial cells of the renal medulla and the medullary collecting ducts. It remains unclear how much of renal prostaglandin synthesis is normally mediated by COX-1 or COX-2 at these various sites. COX-2 may be needed for normal development of the kidney during embryogenesis because homozygous COX-2 knockout mice develop kidneys with abnormal nephrons containing hypotrophic glomeruli and dysplastic tubules. Several studies have detected apparent constitutive expression of COX-2 within the kidney at the following level locations:

- macula densa
- interstitial cells of the papillae
- medullary interstitial cells
- epithelial cells of the thick ascending loop of Henle
- glomerular podocytes

These findings suggest COX-2 has a role in handling sodium and in the regulation of both glomerular filtration and fluid balance. However, it is also highly likely that COX-1, more ubiquitously distributed in the kidney, plays a significant role in all of these processes too.

Whether COX-2 inhibitors would avoid many of the common NSAID-associated renal toxicities was examined in this NDA.

The three clinical pharmacology studies outlined in table 31, were conducted in selected groups of subjects and patients felt to be at risk for adverse renal hemodynamic effects or excretory changes related to use of NSAIDs.

**Table 31. Studies to Assess Effects on Renal Function in NDA 20-998**

| Study | Population | Treatment Groups and Regimens | Treatment Period | Outcome Measures |
|---|---|---|---|---|
| 010 (n=29) | Healthy elderly subjects | - Celecoxib 200/400 mg BID<br>- Naproxen 500 mg BID<br><br>Celecoxib 200 mg BID for five days followed by 400 mg BID for 4.5 days, or naproxen 500 mg BID for 9.5 days; after 7 day washout, crossover to opposite treatment | 10 days | Glomerular filtration rate, urinary PGE2 and 6-keto-PGF1$_\alpha$ excretion |
| 033 (n=42) | Sodium depleted healthy male subjects | - Placebo<br>- Celecoxib 200 mg BID<br>- Celecoxib 400 mg BID<br>- Naproxen 500 mg BID | 6.5 days | Glomerular filtration rate, urinary PGE2 and 6-keto-PGF1α excretion, renal blood flow, plasma renin activity, plasma aldosterone, plasma atrial natriuretic peptide, serum TxB2, fractional sodium, potassium and lithium excretion |
| 036 (n=75) | Patients with chronic renal insufficiency | - Placebo<br>- Celecoxib 200 mg BID<br>- Naproxen 500 mg BID | 6.5 days | Glomerular filtration rate (inulin), urinary PGE2 and 6-keto-PGF1D excretion, plasma renin activity, urinary 11-dehydro-TxB2 excretion, serum TxB2, creatinine clearance, fractional sodium and potassium excretion |

From Text Table 121, ISS.

Principal outcome measures in these studies included glomerular filtration rate (GFR, determined using Glofil, sinistrine, or inulin, and measurement of urinary prostaglandins). Creatinine clearance measurements were also performed as part of two other studies Measurement of prostaglandins in urine has gained general acceptance as a marker of renal prostaglandin production following the original report suggesting their renal origin in healthy women, although a number of methodologic as well as biologic variables can affect urinary prostaglandin measurements in humans. Urine concentrations of $PGE_2$ and 6-keto-$PFG_{1\,\alpha}$ were determined using a combination of chromatographic and GC/ENCI/MS/MS analyses (sensitivity limit of 10 pg/mL) in Studies 010, 036 and 033. Adequate pre-study control assays were conducted to determine accuracy, specificity, sensitivity, and reproducibility of assays. Urine samples were analyzed for 11-dehydro-$TxB_2$ concentrations using radioimmunoassay competition binding assays. The range of calibration was 10 pg/mL to 1000 pg/mL.

The data suggest that COX-2 is present in the human kidney and so represent a potential and plausible candidate to explain any observed clinical toxicity. Cardiac and renal safety was examined in both the short-term, controlled NA trials and in the longer, open-label trial involving approximately 7400 patients with OA and RA. As part of the safety database, the sponsor collected AEs related to both clinical and laboratory measurements. In addition, serial laboratory measurements were obtained from a subset of patients.

**The results (safety, pharmacodynamic) of these trials can be summarized as follows (see cardiorenal consult for details):**

1. **No measurements of acid-base balance (e.g. serum bicarbonate, arterial pH) performed as part of any trial in the NDA. Therefore, an adverse effect of Cx on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia (see below).**
2. **Both Cx and comparator NSAIDs (in short-term trials) inhibited prostaglandin $PGE_2$ and 6-keto-PFG1 α excretion by the kidney to more or less the same extent. Both had significant inhibitory effects on the excretion of urinary prostaglandins when compared to placebo. Cx caused slightly less of a decrease in GFR in one study (010). Both Cx and naproxen inhibited serum renin and urinary (11-dehydro-TxB2) thromboxane levels.**
3. **There was an association between Cx administration and the development of clinically significant edema (especially peripheral edema), similar to comparator NSAIDs, and clearly distinguished from placebo. Both naproxen and Cx cause sodium retention. There was no statistically significant association between ≥1 kg weight gain and the occurrence of 'peripheral edema' in a subset of patients with edema as an AE, although a higher % of both the Cx and active control group patients had both.**
4. **There was an association between Cx administration and the development of worsened hypertension in susceptible individuals, again similar to NSAIDs, and clearly distinguished from placebo.**
5. **There is a definite association between Cx use and an increased incidence of hypophosphatemia, and hyperchloremia compared to placebo and similar to active controls. There was no increase in bony fractures in those individuals with these abnormalities, as might be expected if there is a change in the acid-base balance. An increase in bony fractures has been seen with other drugs with prominent renal tubular toxicities resulting in renal tubular acidosis. The controlled trials were also too short to examine the rate of renal stone formation, which might also increase during renal tubular acidosis. The clinical consequences of these changes remain to be determined.**
6. **There was a trend towards an increase incidence of elevated serum creatinine values and elevated BUN with proteinuria in both the Cx and active control groups relative to placebo. These surrogates for renal toxicity suggest, but do not confirm, a link between Cx use and clinically relevant nephrotoxicity similar to NSAIDs.**
7. **There is no evidence to suggest that Cx has unique renal toxicities not shared by NSAIDs, or evidence of a renal toxicity caused by NSAIDs that occurs at a significantly higher incidence rate with Cx.**
8. **The pattern of AEs reported in both the controlled and the long-term trials is similar to that expected for NSAIDs.**
9. **There were several individuals taking Cx who were withdrawn from the long-term trials because or renal AEs including acute renal failure, edema and worsened hypertension.**
10. **While there were no clear cut cases of Cx-induced renal failure requiring dialysis, it remains to be determined whether severe renal injury will occur at the same rate that is seen with NSAIDs.**
11. **The renal effects of Cx are clearly distinguished from placebo.**
12. **The NDA does not reveal a strong signal pointing towards substantial clinically serious renal disease (i.e. large numbers of patients with acute renal failure requiring dialysis, nephrotic syndrome, papillary necrosis, interstitial neprhritis). This will require a larger database.**

## Hepatic Safety:

Because Cx is metabolized in the liver, a clinical trial in otherwise healthy patients with impaired hepatic function to evaluate the safety and pharmacokinetics of the drug in patients with liver disease. This section will not review this phase 1 (study 016) other than to note that there were no adverse events causing withdrawal, nor were there any serious adverse events or deaths in this study. There were also no laboratory values for which the mean change from Baseline to post treatment was statistically significantly different for these mildly and moderately hepatically impaired subjects.; the interested reader should see the PK review on this topic. Rather, this section will review the overall hepatic effects of Cx in both the controlled and open-label studies.

Comparison of increases in "liver function tests" such as SGOT/AST, SGPT/ALT (the latter felt to be a generally better indicator of damage to the liver), alkaline phosphatase and total bilirubin have been useful screens to help evaluate the overall potential for a drug to cause damage (reversible or not) to the liver. In the NDA, evaluation of increases of these enzyme levels revealed a small percentage of patients with elevations in one or both as seen in Tables 32 and 33 below:

**Table 32. AST by ALT Contingency Tables: Controlled and Open-Label Trials[1]**

| Increase of: | Percent of Patients: Controlled Trials[2] (n) | | | Open-Label |
|---|---|---|---|---|
| | Cx (6188) | Active Control (2667) | Plc (1786) | Cx (4404) |
| ALT and AST < 3 ULN | 1.7 | 2.7 | 1.5 | 2.7 |
| ALT and AST ≥ 3 ULN | 0.08 | 0.30 | 0.22 | 0.07 |

3.) Data from Table 2.1 (N49-98-17-819)

*4.)* Includes studies 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 071 and 087.

**Table 33. Alkaline Phosphatase (AP) by Total Bilirubin (TB) Contingency Table[1]**

| Increase of: | Percent of Patients: Controlled Trials[2] (n) | | | Open-Label |
|---|---|---|---|---|
| | Cx (6182) | Active Control (2664) | Plc (1784) | Cx (4404) |
| TB <1.8 ULN: AP < 3 ULN | 2.0 | 2.3 | 1.5 | 2.5 |
| TB ≥ 1.8 ULN: AP ≥ 3 ULN | 0.0 | 0.0 | 0.05 | 0.0 |

1.) Data from 3.1 (N49-98-17-819)

2.) Includes studies 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 071 and 087.

As can be seen by these contingency tables, and given the caveats regarding how well these enzymes function as surrogates of serious liver and/or biliary tract disease, there does not appear to be a significant degree of liver toxicity associated with the use of Cx in either short-term or longer-term administration.

Analysis of adverse events in the North American and International trials (Table 11.3, ISS) for liver and biliary system disorders includes the following:

- AG Ratio Abnormal Biliary Pain Bilirubinemia Cholecystitis
- Cholelithiasis Gall Bladder Disorder Hepatic Function Abnormal
- Hepatomegaly Jaundice SGOT increased SGPT increased

There were no statistically significant differences between Cx and placebo for any of the disorders listed above (N for Cx=3512, N for placebo=1864). However, there were statistically significant differences (p=0.05) between Cx and the active controls for SGOT increased (Cx=8/3562 patients vs. active control=22/2768 patients) and for SGPT increased (Cx=14/3562 vs. 28/2768). Of interest, there were opposite results for SGOT and SGPT increases when Cx was compared to placebo in males vs. females in the North American arthritis trials (Table 19.3, ISS). In particular, a greater percentage of male placebo patients had increases of SGOT and SGPT than Cx subjects (0.9 vs. 0.3 and 1.1 vs. 0.4, respectively). The result for female placebo patients compared to Cx treated patients was reversed for SGOT and SGPT increases (0.2 vs. 0.4 and 0.2 vs. 0.6, respectively).

Fifteen (15) patients were withdrawn due to liver and biliary system disorders in the combined North American and International arthritis trials (Table 11.4, ISS). There was one patient in the placebo group who withdrew, two each in the celecoxib 100 mg and 200 mg BID dose groups, and 10 in the active control group. The four causes of withdrawal included gall bladder disorder, hepatic function abnormal, SGOT increased or SGPT increased. There was an additional case (pt. 110) of withdrawal in one of the PK trials (003) for increased SGOT, the PI was uncertain as to the relationship to Cx (20 mg BID). This subject was rechallenged (after laboratory results normalized) with Cx and had no recurrence of abnormal laboratory values. Elevated laboratory values, including liver function tests, also resulted in an entire treatment arm being repeated in Study 001 to corroborate or refute the clinical laboratory abnormalities that occurred in the first panel. The subjects who were enrolled in the replicate study had no clinically significant laboratory abnormalities. Analyses of these findings (Table 11.5, ISS) in the controlled arthritis trials revealed no statistically significant differences between the treatment groups in terms of withdrawal rates.

There were 10 serious adverse events related to the hepatic and biliary system which are listed in table 34 below:

**Table 34. Serious Adverse Events Related to the Hepatic or Biliary System**

| Event | Pt number | Age/sex | Treatment | Caused Withdrawal |
|---|---|---|---|---|
| Cholecystitis | 021-US0059-0642 | 72/F | Cx 100 BID | Yes |
| Cholecystitis | 023-US0026-1137 | 43/F | Placebo | No |
| Gallbladder disorder | 021-US0099-0180 | 52/F | Naproxen 500 BID | No |
| Gallbladder disorder | 021-US0191-1334 | 67/F | Naproxen 500 BID | Yes |
| Cholelithiasis | 024-US0001-0010011 | 46/M | Cx 200 mg BID | No |
| Cholelithiasis | 024-US0017-0170033 | 52/M | Cx 100 mg BID | Yes |
| Cholelithiasis | 024-US0022-0220054 | 60/F | Cx 400 mg BID | Yes |
| Cholelithiasis | 024-US028-0280088 | 35/F | Cx 100 mg BID | No |
| Cholelithiasis | 024-US073-0730010 | 38/F | Cx 200 mg BID | No |
| Cholelithiasis | 024-US095-0955003 | 44/M | Cx 200 mg BID | No |

As can be seen in table 34, patients with serious adverse events ranged in age from 35 to 72 years; seven were female and three were male. In no case did the Investigator consider that the event was related to study drug. Two of the patients who developed serious adverse events related to the hepatic and biliary system received active control, one received placebo, and the remaining seven received celecoxib. All but four were enrolled in the long-term arthritis trial (024), three were enrolled in Study 021, and one in Study 023. One patient died as a result of complications to a gallbladder disorder. This was a 67-year-old man who had a necrotic gallbladder and subsequently succumbed to a myocardial infarction 14 days after the gallbladder event was identified (Patient 021-US0191-1334). He received naproxen 500 mg BID during Study 021.

As discussed above, the clinical laboratory results that were evaluated were SGOT, SGPT, total bilirubin, PT, PTT, alkaline phosphatase, and albumin. There were few extreme laboratory values for any treatment group for any of the liver function tests. Only differences in incidences of alkaline phosphatase in the International studies reached statistical significance (0.0% for celecoxib vs. 1.2% for active control). Analysis of mean changes in laboratory variables revealed no clinically significant changes in any hepatic laboratory parameter from Baseline to final visit.

**In summary,** it does not appear that Cx is associated with alterations in liver function or with adverse events (including serious) due to liver or biliary tract disease. Celecoxib is metabolized in the liver, and while clearance of Cx is reduced in the presence of moderate liver disease (see PK review), the tolerability of the drug does not seem affected. However, since patients with severe liver disease were not studied in the NDA, such patients should not be given Cx until further studies confirm safety and/or give recommendations regarding safe dosing in this populations. Liver function test abnormalities (AST, ALT, bilirubin, and alkaline phosphate) were rare, and seen at rates more similar to placebo than the NSAID controls.

***Reviewer's comment: There was nothing of significance added with regards to hepatic events with the 120-day Safety Update.***

## Endocrine or Metabolic Safety:

As the understanding of the distribution of COX-2 evolves, it is now appreciated that this enzyme may be constitutively expressed in the pancreas. Since, the Sponsor felt there were no preclinical findings suggesting endocrine or metabolic effects of celecoxib, no clinical studies were performed to specifically assess the effects of celecoxib on the endocrine system. For the pancreas, this could have included evaluations of serum (total) amylase or lipase to look for episodes of acute pancreatitis, but these were not measured; the incidence of drug induced pancreatitis from either NSAIDs or sulfonamide containing drugs is very rare (literature estimates of <0.01%).

Adverse event findings from clinical trials were reviewed by the Sponsor for the following W.H.O.a.r.t. body systems: endocrine system, male and female disorders (excluding neoplasms specific to gender), and metabolic and nutritional disorders. Adverse event findings for at risk subgroups (i.e. age, gender, race, weight, pertinent medical history, concomitant medications such as oral hypoglycemic agents, insulin, lipid-lowering drugs, thyroid medications, and estrogens) were analyzed. This included laboratory data (calcium, inorganic phosphorus, uric acid, glucose, and cholesterol, glucose in the urine). The analyses of the data described above suggests that Cx has no clinically apparent effects on the metabolic and endocrine system. As expected with multiple analyses of large databases, sporadic changes in laboratory parameters or differences between groups in incidence rates of occasional adverse events were observed, but there was no obvious pattern of clinical effect with Cx treatment.

In the crossover trial (039) that studied the effect of Cx on the PK profile of glyburide in patients with well-controlled NIDDM, there was one (11%) placebo treated subject (9102) in the glyburide 5 mg QD group withdrew from the study because of mild hypoglycemia on Day 7 (<60 mg/dL) before receiving Cx. There were no serious adverse events and no deaths during this short study.

Analysis of adverse events (Table 6.3.1, ISS) in the North American trials for Cx (100 and 200 mg BID) did not reveal any statistically significant differences between Cx and placebo, or Cx and active control for any parameters listed under WHO a.r.t. Metabolic and Nutritional Disorders (includes such listings as diabetes mellitus, diabetes mellitus-aggravated, glycosuria, hyperglycemia, hyperlipidemia, etc.). The results were the same when the comparisons were between Cx 400 mg BID and placebo or active control (Table 6.3.2, ISS). Of note, there were up to 0.5% of patients listed with abnormal stools in the Cx-treated patients (100/200/400 mg) whereas there was 0.1% in the placebo group and none in the active controls; these differences were not statistically significant.

Serious adverse events that might have related to the pancreas during the controlled arthritis trials included one case of pancreatitis (study 021, pt. 0642) in a 72 y/o female secondary to gallstones (not attributed to treatment by PI or Searle monitor). She had

been taking Cx 100 mg BID and was withdrawn from the trial. One patient (study 054, pt. US0157-1233) was withdrawn secondary to abdominal pain but nothing else to suggest the pancreas as the source. One patient taking Cx 100 mg BID was withdrawn for hyperglycemia (study 042, pt. UK0016-0433). Screening urinalysis indicated glycosuria and blood glucose level of 9.56 mmol/L (not indicated as fasting or random). At the week 4 visit, the glucose level had increased to 23.12 mmol/L. Both the PI and Searle monitor listed as possibly related to Cx. One patient in the placebo group was withdrawn because of hypoglycemia.

In the long-term, open-label study (024), two patients (024-US0030-0300024 and 024-US0125-1250007) had a SAE listed as aggravated diabetes mellitus; neither was removed from the trial.

Comparison by shift table analysis (Table 35, below) for glucose values (baseline to final values) in the NA arthritis trials for Cx (Text Table 83, ISS) revealed the following:

**Table 35. Shift Table of Glucose Values in North American Trials**

| Glucose | Cx 100/200 mg BID | Placebo | Active Control |
|---|---|---|---|
| Low | 0 | 0 | <1% |
| High | 3.7% (from normal) | 4.1% (from normal) | 3.2% (from normal) |

However, analysis of mean change for glucose in the 12-week NA arthritis trials with Cx at both 100 and 200 mg BID as well as 400 mg BID compared to active control revealed no statistically significant differences (Test Table 78, ISS). Analysis of extreme laboratory values for glucose (< 2.22 mmol or >19.4 mmol) in patients with diabetes or taking oral antidiabetic agents, oral steroids, or insulin revealed inconsistent findings but no significant differences between Cx and active controls . There were suggestions that Cx behaved differently in patients older than 65 years than those that were younger as noted below in table 36:

**Table 36. Glucose Values in Elderly vs. Younger Patients**

| | <65 years | | >65 years | |
|---|---|---|---|---|
| | Cx (n=1587) | Placebo (n=832) | Cx (n=916) | Placebo (n=495) |
| High Glucose (maximum value) | 0.8% | 0.2% | 0.4% | 1.2% |

Interestingly, Cx also seemed to protect against extreme high glucose values in patients taking steroids, relative to placebo. Comparison of extreme high glucose values in blacks, on the other hand, suggested Cx was associated with a higher incidence in patients receiving either active controls or placebo; this pattern was not seen in Caucasians (Text Tables 74 and 75, ISS).

Finally, an analysis of urine glucose values in the NA arthritis trials reveals the following (Table 37):

**Table 37. Urine Glucose Values in North American trials**

| Abnormality | Placebo N=1136 | Cx N=2256 | Active Control N=1099 |
|---|---|---|---|
| Urine Glucose >trace | 2.6% | 3.4% | 2.0% |
| Urine Glucose >1+ | 1.8% | 2.7% | 1.5% |
| Glycouria and any other renal lab abnormality | 0.4% | 0.1% | 0.5% |
| Urine glucose >trace Non-diabetics | 2.4% | 2.4% | 2.3% |

For the interested reader, there is a more detailed discussion of these renal laboratory results in the cardiorenal consultation (p.74-77).

**In summary,** it appears that the endocrine/metabolic safety profile of celecoxib is certainly no worse than the active controls. There were no consistent adverse event findings for these body systems. Endocrine/metabolic serious adverse events, withdrawals due to adverse events, and clinical laboratory abnormalities with Cx (especially as discussed for pancreatic endocrine functions) did not indicate any pattern of consistent drug association. Although there may be suggestions of some effects, adequate interpretation is difficult due to limited patient numbers or events.

## Drug-drug interactions:

Four interaction trials were conducted with drugs that are metabolized in the liver. These included studies in patients with noninsulin dependent diabetes taking glyburide (Study 039), and in healthy subjects who were given fluconazole and ketoconazole (Study 072), phenytoin (Study 050), or tolbutamide (Study 051). Further details and results of these trials can be found in the PK review. However, the current Agency labeling is as follows:

- **General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. In vitro studies indicate that celecoxib, although not a substrate, is a weak inhibitor of cytochrome P450 2D6. Therefore, there is a low probability for an in vivo drug interaction with drugs that are metabolized by CYP2D6.**

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

- **Lithium: No clinically significant differences were seen in the mean steady-state lithium PK parameters between lithium 450 mg BID given alone or with CELEBREX in healthy adults. Celecoxib treatment significantly increased average steady-state plasma concentrations of lithium by about 17%. However, in none of the 24 subjects studied did the lithium concentration exceed the accepted upper range of 1.5 mEq/L. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.**

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

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

- **Aspirin: CELEBREX has been administered to patients taking aspirin up to 325 mg per day. Low doses of aspirin have been associated with ulcers. Thus concomitant use of CELEBREX with aspirin may result in an increased rate of GI ulceration compared to that with CELEBREX used alone.**

- **Methotrexate: In an interaction study of RA patients taking methotrexate, CELEBREX did not affect the pharmacokinetics of methotrexate. Methotrexate: In an interaction study of RA patients taking methotrexate, CELEBREX did not affect the pharmacokinetics of methotrexate.**

## Geriatric Studies:

Characterization of the safety profile of Cx in the elderly (>65 years) is important since the elderly arthritis population is one of the larger patient subgroups who will use the drug. Adverse events among the elderly may be more frequent than in the non-elderly for several reasons, including differences in exposure due to metabolic differences or reduced body size, increased presence of other illnesses, or the increased use of other medications. Elderly patients are also less able to tolerate significant adverse events when they occur, such as GI bleeding.

In the NA arthritis trials, 37% (2117 of 5704) patients were ≥65 years (Table 6.1, ISS). This compares to 39% of the placebo patients (731/1864) and 35% in the active control (737/2098). Looking at the placebo and active-controlled NA trials (020, 021, 022, 023, 054) only, 11% (78/690), 11% (119/1131), 10% (113/1125) and 4% (15/434) were ≥75 years in the Cx 50 mg BID, 100 mg BID, 200 mg BID, and 400 mg BID groups, respectively. This compares to about 9% in the placebo groups (102/1136) and 10% (105/1099) in the active control groups (Text Table 141, ISS).

The safety profile of Cx in the elderly was examined both from specific studies conducted to evaluate the pharmacokinetics and renal effects of Cx in the elderly (010; see cardiorenal consult for more details) and from the arthritis studies. Study 010 suggested that Cx did not affect the GFR in healthy elderly subjects. Adverse events, rates of withdrawals, effects on clinical laboratory tests and vital signs were all examined. Elderly females, because of their smaller size and slightly increased exposure as shown in Study 015 (see PK review for additional details on this study), were also analyzed separately to rule out any important increased safety risk in this subgroup. Despite PK differences, there were no clinically significant differences in the pharmacodynamics between elderly and younger subjects, as measured by GFR and platelet aggregation. There also were no clinically significant differences in the adverse event profiles between elderly and young subjects.

Table 38 below (taken from Text table 140, ISS), although taken from these short trials, (010, 015) illustrates some of the overall findings regarding AE results with consideration of age. In general, there is an increased incidence of AEs in the elderly as compared to younger subjects. This increase is not, however, universally true across body systems. Adequate interpretation across all dosage levels of Cx is complicated by the fact that there are small numbers of patients in the >75 year groups (as noted above). Also, there are AEs that are increased with increasing dose in the elderly; but this again is by no means a consistent finding (Table 31.4.2, ISS).

**Table 38. Cumulative Incidence of AEs in Elderly (Study 010, 015)**

| | Young Subjects (only in Study 015) | Elderly Subjects in Both Trials | | Cumulative Incidence in Elderly: Both Trials and Both Cx doses |
|---|---|---|---|---|
| Adverse Event | Cx 200 mg BID (N= 26) | Cx 200 mg BID (N=50) | Cx 400 mg BID (N=26) | (N=76) |
| Headache | 1 (3.8) | 5 (10.0) | 0 (0.0) | 5 (6.6) |
| Arthralgia | 1 (3.8) | 3 (6.0) | 1 (3.8) | 4 (5.3) |
| Constipation | 1 (3.8) | 2 (4.0) | 2 (7.7) | 4 (5.3) |
| Dizziness | 1 (3.8) | 3 (6.0) | 1 (3.8) | 4 (5.3) |
| Flatulence | 0 (0.0) | 1 (2.0) | 2 (7.7) | 3 (3.9) |
| Edema peripheral | 0 (0.0) | 0 (0.0) | 3 (11.5) | 3 (3.9) |
| Injection site reaction | 0 (0.0) | 3 (6.0) | 0 (0.0) | 3 (3.9) |
| Upper resp tract infection | 0 (0.0) | 2 (4.0) | 1 (3.8) | 3 (3.9) |
| Abdominal pain | 2 (7.7) | 0 (0.0) | 1 (3.8) | 1 (1.3) |
| Back pain | 0 (0.0) | 2 (4.0) | 0 (0.0) | 2 (2.6) |
| Somnolence | 0 (0.0) | 2 (4.0) | 0 (0.0) | 2 (2.6) |

Tables 39 and 40 (taken from text Tables 142 and 143, ISS) show adverse events for which the risk difference between Cx and placebo or between Cx and active control was statistically significantly different between elderly and younger patients:

**Table 39. Risk differences in Elderly: Celecoxib vs. Placebo**

| | <65 years | | ≥ 65 years | |
|---|---|---|---|---|
| | Cx | Placebo | Cx | Placebo |
| No. treated | 2143 | 1133 | 1369 | 731 |
| Coughing | 1.8 | 1.7 | 1.9 | 0.5 |
| Hypertension, aggravated | 0.2 | 0.4 | 1.1 | 0.3 |
| Tinnitus | 0.7 | 0.2 | 0.3 | 0.5 |

**Table 40. Risk differences in Elderly: Celecoxib vs. Active control**

| | <65 years | | ≥ 65 years | |
|---|---|---|---|---|
| | Cx | Active control | Cx | Active control |
| No. treated | 1893 | 1361 | 997 | 737 |
| Abdominal pain | 5.4 | 7.6 | 4.0 | 9.2 |
| Dyspnea | 0.8 | 0.4 | 0.6 | 1.5 |
| Pain | 1.2 | 1.9 | 1.3 | 0.4 |
| Rash | 2.3 | 2.2 | 3.0 | 1.1 |
| Sinusitis | 6.4 | 6.2 | 4.1 | 1.6 |

Again, the AEs in the tables above (which includes only trials 020, 021, 022, 023, and 054) seem to represent the pattern of AEs seen overall and may point to the reasons for some of the differences between Cx and placebo (i.e. aggravated hypertension) or between Cx and active control (i.e. rash).

In looking at elderly females, a group that may be (based on study 015) at the highest risk, it is interesting to note that overall, Cx-treated females >65 years had fewer adverse events than those <65 years (59.4% compared to 64.2%, $p<0.05$) (Table 19.5, ISS). The risk difference (for 20 events, $p \leq 0.05$) for pain, hypertension aggravated, nausea, coughing, and rash were higher for Cx than placebo for elderly females (Text Table 144, ISS). On the other hand, in the active control comparisons,

only the risk difference for pain was higher for elderly females than younger females. However, the percentage of elderly females receiving Cx who complained of pain and nausea appeared to be similar to the percentage of younger females with these complaints. Comparison of adverse events, in general, does not suggest any clinically meaningful difference in incidence between elderly females and non-elderly females treated with celecoxib.

Considering AEs causing withdrawal, (Table 31.4.3, ISS), there were no clinically significant findings in the patterns of withdrawals due to Cx or due to dosage of celecoxib. The incidence of AEs causing withdrawal in the long-term open-label trial (Study 024, Table 31.4.4, ISS) also suggests the pattern of withdrawal in the elderly is similar to the non-elderly.

Review of the subgroup analyses of adverse events by age (Tables 19.1 and 19.2, ISS) reveals an apparent excess of myocardial infarction (MI) in Cx-treated elderly patients (see cardiorenal consult and cardiovascular section of this review for more details on cardiovascular events with Cx). There were seven events (0.5%) in the elderly Cx patients compared to one event (0.1%) in the elderly placebo group and two events (0.3%) in the active control patients. Only the difference between Cx and placebo was statistically significant (p=0.046). However, no apparent pattern implicating Cx is consistently evident from reviewing these cases. For example, patients often had one or more other cardiac risk factors or active symptoms prior to treatment; not unexpectedly for the age of the population studied or suggesting that this finding may have been due to chance.

In reviewing the database for other evidence of increased vascular occlusive-type events, the incidence of cerebrovascular events in the elderly was reviewed. There was no apparent excess of cerebrovascular events in the elderly Cx patients, with two elderly patients in each of the Cx, placebo, and active control groups.

Because the elderly may tolerate UGI bleeding less well than the non-elderly, the incidence of endoscopically detected gastroduodenal ulcers with Cx in this age group was addressed. Over 800 patients >65 years underwent endoscopy to evaluate the gastroduodenal mucosal effect to Cx, placebo or active control therapy. Text Table 146 The crude ulcer rates observed at endoscopy in the different age groups are shown in table 41 (from Text Table 146, ISS):

**Table 41. UGI Endoscopic Rates in Elderly: Study 021, 022, 062, 071**

| | Age | |
|---|---|---|
| Treatment group | <65 years | ≥65 years |
| Placebo | 6/142 (4.2%) | 2/63 (3.2%) |
| Cx | 59/983 (6.0%) | 35/414 (8.4%) |
| Active control | 166/748 (22.2%) | 105/331 (31.7%) |

These data certainly suggest that for the >65 age group, the crude ulceration rates with Cx are not substantially increased with age and are were well below the rates observed with the active controls.

Mean changes from baseline for BUN, hematocrit, hemoglobin and platelet counts from the placebo- and active-controlled arthritis trials (Studies 020, 021, 022, 023, and 054) and the long-term, open-label trial divided according to gender and age >65 years or below do not seem to indicate significant differences between older or younger patients. The decreases noted in platelet count in the female population appear to be more pronounced than in male patients. However, the magnitude of the changes is <5%, and when females in the open-label trial were evaluated for the effects of longer exposure, there was no pattern of continued decline in platelet count; in fact the counts tended to rise back toward baseline after 12 weeks of treatment.

**In summary,** the safety profile of Cx in the elderly is not different from that in non-elderly patients. The nature and incidence of adverse events is similar to that seen in younger patients, and although there are generally somewhat higher incidences of adverse events, the withdrawal rate due to adverse events is not different between the young and the elderly. The data from the entire analysis of the elderly population demonstrates that Cx is safe and well tolerated in the elderly, and poses no apparent additional safety considerations which do not apply to the younger age group.

## Cardiovascular Safety

***Reviewer's comment: For a detailed examination of the results of Cx on cardiovascular safety, the interested reader is encouraged to read the cardiorenal consult.***

The association of COX inhibitors with cardiovascular disease is based on their effects upon prostaglandins, primarily in the kidney, but also to a lesser extent, in platelets and in vascular endothelium. It had been hypothesized that these effects are mostly due to inhibition of COX-1, resulting in fluid retention and hypertension. However, as noted in the cardiorenal consult, Cx is also associated with edema and worsened hypertension. As discussed in one of the consults from the Division of GI and Coagulation Drug Products, Cx does not seem to affect platelet function (aggregation) at, and above, therapeutic doses

This cardiovascular effects of Cx were addressed by following W.H.O.a.r.t. body systems: General Cardiovascular Disorders, Heart Rate and Rhythm Disorders, Myo/Endo/Pericardial and Valve Disorders and Vascular (Extracardiac Disorders). In addition, pertinent adverse events from other body systems, such as hypertension, were reviewed. Serious cardiovascular events, the effects of medical histories and concurrent medications, pertinent vital sign and laboratory data were also reviewed.

Adverse Events

Table 42 below presents the cardiovascular adverse events for which there was a ≥1% incidence in the NA arthritis trials.

**Table 42. Cardiovascular AEs: Incidence ≥1% in North American arthritis trials[1]**

| | | Celecoxib (mg) | | | | | |
|---|---|---|---|---|---|---|---|
| Adverse Event | Placebo | 50 BID | 100 BID | 200 QD | 200 BID | 400 BID | Active Control |
| No. Treated | 1864 | 690 | 1779 | 453 | 1914 | 615 | 2098 |
| Any event | 53 (3.0) | 27 (3.9) | 74 (4.2) | 22 (4.9) | 123 (6.4) | 39 (6.3) | 120 (5.7) |
| Edema peripheral | 21 (1.1) | 15 (2.2) | 27 (1.5) | 13 (2.9) | 49 (2.6) | 15 (2.4) | 45 (2.1) |
| Hypertension | 5 (0.3) | 2 (0.3) | 11 (0.6) | 1 (0.2) | 20 (1.0) | 3 (0.5) | 14 (0.7) |

1. From Table 32.1.1 (ISS). Includes trials 012, 013, 020, 021, 022, 023, 047, 054, 060, 062, 071, and 087.

As can be seen, peripheral edema was the most common cardiovascular adverse event. There is no obvious dose-response relationship; overall incidence with Cx appears similar to the active control. Further analysis, (Text Table 154, ISS) revealed there was no statistically significant difference in incidence of peripheral edema between Cx and active control, but there was between Cx and placebo (p=0.007). The peripheral edema associated with Cx was reported as mild to moderate in severity in 97% of cases, and in only 17% was judged to be "probably related" by the Investigator. Of note, generalized edema, a potentially more meaningful indication of clinically important fluid retention (which was coded only when CRF text stated "generalized" or "body" edema), was significantly more frequent in patients receiving active controls than in

Cx patients (active control 0.5% vs. 0.1% for Cx, p=0.031). The differences in the incidence of hypertension between treatment groups (in this comparison) was not statistically significant for Cx vs. placebo or for Cx vs. active control. A related, but less frequent, adverse event, "hypertension aggravated" also was also not significantly different in incidence between Cx and placebo, or Cx and active control in these comparisons. There were no events for which there was a ≥1% incidence in any treatment group for patients who withdrew due to a cardiovascular adverse event.

The next table (from Text Table 155, ISS) summarizes the incidences of cardiovascular AEs by body systems and by time interval in the long-term, open-label trial (024).

**Table 43. Cardiovascular AEs: Incidence ≥1% in Long-Term Trial (024)[1]**

| Adverse Events | | Dosing Intervals (Days) | | | | | |
|---|---|---|---|---|---|---|---|
| | No.(%) of Pts with Event | 1-90 | 91-180 | 181-270 | 271-360 | 361-450 | 451-540 |
| No. treated | 4499 | 4499 | 3545 | 2373 | 1576 | 970 | 294 |
| Adverse Event | | | | | | | |
| Hypertension | 77 (1.7) | 0.8 | 0.5 | 0.6 | 0.5 | 0.4 | 0.0 |
| Edema peripheral | 172 (3.8) | 2.6 | 0.9 | 0.7 | 0.7 | 0.1 | 0.0 |
| WHO art body system/disorder | | | | | | | |
| Cardiovascular, general | 29 (0.6) | 0.2 | 0.2 | 0.2 | 0.5 | 0.0 | 0.0 |
| Heart rate/rhythm disorders | 65 (1.4) | 0.8 | 0.4 | 0.4 | 0.4 | 0.3 | 0.0 |
| Myo/end/pericardial and valvular disorders | 58 (1.3) | 0.6 | 0.5 | 0.4 | 0.5 | 0.3 | 0.0 |
| Vascular (extracardiac) | 57 (1.3) | 0.5 | 0.4 | 0.6 | 0.3 | 0.2 | 0.0 |

1. From Tables 9.2 and 9.5 (ISS).

As with many other adverse events in this trial, the highest incidence of peripheral edema occurred in the first 90 days of dosing with celecoxib, during which time the patients were seen more frequently than in later intervals. Peripheral edema was, however, the only cardiovascular adverse event for which there appeared to be a temporal relationship to the onset of dosing. The prevalence of peripheral edema remained essentially constant at 2.6% throughout the first year in the trial, and fell slightly to 1.7% at 451-540 days. The cases of peripheral edema resulted in a low incidence of withdrawals (<0.1%) for all treatment intervals (Table 9.6, ISS).

The only cardiovascular-related AEs that occurred in ≥1% in the international arthritis trials were hypertension and peripheral edema (hypertension, 0.9-1.2% with Cx vs. 0.0-1.5% with active controls: peripheral edema, 2.0-3.4% with Cx vs. 1.5-2.3% with active controls).

> ***Reviewer's comment: Serious adverse events, withdrawals and deaths related to the cardiovascular system as well as potential interactions with various drugs classes (i.e. ACE inhibitors, beta blockers, etc.) are discussed in detail in the cardiorenal consult.***

Comparison of increases in BUN and creatinine (Cr) have been useful screens to help evaluate the overall potential for a drug to cause damage (reversible or not) to the kidney. In the NDA, evaluation of increases of these laboratory values has resulted in the following (Table 44):

**Table 44. BUN (mmol/L) by Creatinine (Cr -μmol/L) Contingency Table[a]**

| Increase of: | Percent of Patients: Controlled Trials[b] (n) | | | Open-Label |
|---|---|---|---|---|
| | Cx (5538) | Active Control (2025) | Plc (1786) | Cx (4404) |
| Cr < 159 and BUN ≥ 14.3 | 0.3 | 0.2 | 0 | 0.2 |
| Cr ≥ 159 and BUN ≥ 14.3 | 0.04 | 0.15 | 0.06 | 0.18 |

a.) Data from Table 4.1 (N49-98-17-819)

*b.)* Includes studies 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 071 and 087.

These results are consistent with that of the other renal safety results which suggest that, overall, event rates for potentially serious events are low but that Cx is more like the active control than placebo in this regard.

The overall cardiovascular safety profile of Cx is mostly unremarkable. However, the increased rate of peripheral edema compared to placebo (2.1% vs.1.1%) are real and are similar to the incidence seen with active control (2.1%). This edema was generally mild, and usually not attributed to treatment by the Investigator. The edema did not appear to be significantly associated with or exacerbated by preexisting cardiovascular disease or use of concomitant cardiovascular medications.

**In conclusion**, as noted under the "Deaths" section of this review, and in the cardiorenal consult, myocardial infarction was noted to occur at a higher rate in Cx than placebo patients. In the long-term trial, the predominate (90%+) cause of death for patients taking Cx at any dose was cardiovascular. The majority of these deaths represented progression of previously known CV disease. The demographics of the subjects in the controlled trials, as estimated from ICD-9 codes, reveals that about 35-40% of the subjects had hypertension, 15% had a history of significant cardiac disease (i.e. MI, angina pectoris), 7-8% were diabetic, 7-10% were hyperlipidemic, and 3-4% had significant renal disease. No information about smoking history is available. Examination of the Kaplan-Meier survival curves (see cardiorenal consult) for both the controlled and long-term trials, suggests there is no apparent relationship between any given duration of exposure to Cx and increased mortality.

Nonetheless, there may are suggestions of a dose-response relationship between CV mortality and Cx use although the database is not sufficient to answer this question either way. It is interesting to remember, however, that Cx is not associated with antiplatelet effects. Therefore, it seems reasonable to remind physicians that Cx does not provide cardiovascular prophylaxis. Cardiovascular serious adverse events, withdrawals, vital

signs and clinical laboratory test parameters abnormalities were unremarkable with Cx and did not seem to indicate any pattern of drug association.

The administration of Cx cannot be linked to any rare or unusual cardiac toxicities based on the available data. For some AEs, including arrhythmias and overall CV mortality, the data are inadequate to either exclude or confirm and adverse effect of Cx. The available data do suggest the effects of Cx are similar to NSAIDs with regard to the "cardiac" effects of hypertension and edema (see Renal Safety section).

## Skin Safety:

The NDA did not include any studies with endpoints specifically related to effects on the integumentary system. However, This four aspects of the adverse event data from the clinical trials did attempt to address this issue:

- **occurrence of AEs related to skin and appendages**
- **subgroup analyses of AEs with respect to presence or absence of medical history or medication use relevant to the skin and appendages**
- **occurrence of withdrawals and serious adverse events relating to skin and appendages**
- **occurrence of select clinical laboratory test elevations that could be associated with dermatologic adverse events**

Review of the cutaneous reactions associated with Cx was assisted by a consultant academic dermatologist experienced in the interpretation of drug-related cutaneous adverse events.

Celecoxib has a sulfa moiety in its chemical structure, and therefore as a precaution patients with sulfa allergies were excluded from clinical trials.

The laboratory tests of particular interest that were considered to be possibly related to the integumentary body system are BUN, creatinine, and eosinophil counts. Specifically, elevated BUN and creatinine could be associated with pruritus and urticaria (in the case of uremia), and eosinophilia could be associated with rash (in the case of a systemic allergic response). Therefore, the number of patients who had both the clinical laboratory abnormality(s) and a skin adverse event(s) were identified for Cx, placebo, and active control treatment groups.

As noted elsewhere in this review, although the incidences of skin adverse events was low, there was a higher incidence in pruritus, rash, and erythematous rash for celecoxib 400 mg than for lower doses of celecoxib, placebo and active control (i.e. 2.9%, 3.4% and 1.1% respectively for Cx 400 mg BID vs. 1.6%, 2.1%, and 0.1% respectively for the lower doses of Cx; Text Table 177, ISS). Statistical analyses of AE incidences among treatment groups for Cx 100 mg BID and 200 mg QD and BID revealed only one

difference; this occurred for increased sweating between Cx (n=2, or <0.1%) and active control (n=7, or 0.3%). Similarly, statistical analyses of AE incidences among treatment groups for Cx 400 mg BID revealed only one skin-related event difference; this occurred for pruritus between Cx 400 mg (n=18, or 2.9%) and placebo (n=8, or 1.3%).

Other cutaneous reactions not classified under the WHO coding system as a skin and appendage disorders include stomatitis and vasculitis. The incidence of vasculitis was rare (only one case of mild severity) in all treatment groups although there were a few other cases suggestive of vasculitis (see Safety Review by Villalba). Stomatitis occurred in ≤1.2% of Cx patients compared to 1.3% of NSAID control patients and 0.5% of placebo patients. There was no association of stomatitis in Cx-treated patients with the use of methotrexate or DMARD drugs.
The only incidence of skin-related AEs causing withdrawal in≥1% of patients in the North American arthritis trials was rash (again higher than the incidences for either placebo or active controls).

Overall, there was a higher incidence of skin-related withdrawals from study participation for patients who received Cx than for patients who took either placebo or active control. Analyses of AEs causing withdrawal between Cx 100 mg BID and 200 mg QD and BID and placebo or active control revealed only five AEs for which there was a statistically significant difference between treatments, and that three of these were related to skin. These were a statistically higher incidence of urticaria for Cx patients than placebo patients, and statistically significantly higher incidences of rash and pruritus for Cx patients than for active control patients. There were no skin and appendages adverse events that were statistically significantly different between groups Cx 400 mg and either placebo or active control.

For the 4499 patients who were enrolled in the long-term, open-label trial, the overall incidence was 2.6% for pruritus and 4.2% for rash. The incidences of pruritus and rash were greatest in the first 90 days of dosing: 2.2% and 3.0%, respectively. For the time intervals following the first 90 days after dosing began, the occurrence of new pruritus and rash adverse events ranged from 0.0% to 0.8%. In this long-term trial, the incidences of withdrawal due to pruritus and rash ranged from 0.0% to 0.4% for any dosing interval approximately half that of the 12-week controlled NA arthritis trials.

With the exception of one serious adverse event in the controlled clinical trials and two serious adverse events in the long-term, open-label trial, most SAEs relating to the skin and appendages were related to cancer (especially basal cell, Text Table 181, ISS).

In the analysis by concomitant use of sulfa-containing drugs, there were no statistically significant risk difference between Cx and placebo. There was a higher incidence of rash among patients who took Cx and a sulfa drug (7.7%) than among patients who took active control and a sulfa drug (0.0%): this was a statistically ($p \leq 0.05$) significant difference (Text Table 182, ISS). Presence of a drug dermatitis history did not contribute

to any statistically significant differences between Cx and placebo or between Cx and active control.

Analyses performed on all NA arthritis trials looking for patients who had pruritus or urticaria or rash and eosinophilia (>0.7x10 $^9$/L) revealed only one patient that met these criteria; this was a patient who received celecoxib 200 mg. There were no statistically significant differences between any of the treatment. Similarly, analysis for patients who had pruritus or urticaria and at least one laboratory abnormality (BUN ≥14.3 mmol/L or creatinine ≥159 µmol/L) also revealed only one patient who met these criteria. This was a 70-year-old female (patient 047-US0033-0030) receiving Cx 400 mg BID who developed hemolytic uremic syndrome due to repeated dosing with quinine sulfate. Her pruritic symptoms were caused by the uremia, and resolved with discontinuation of quinine and resolution of the uremia. There were no patients who had all four of these AEs (dermatitis/pruritus/rash/urticaria). These findings would suggest that there were no subclinical events of potential clinical significance in any of the NA arthritis trials.

**In summary**, rashes and related cutaneous reactions were among the more frequently noted AEs associated with Cx treatment. The rashes were generally mild in severity, and often associated with urticaria or pruritus. There was no distinguishing morphologic pattern characterizing the possible Cx-associated eruptions. The majority of rashes were not described as "erythematous" or "psoriaform" in nature. Although of mild severity, rash was nonetheless the single most common reason for withdrawal from study treatment, with a rate of approximately 1% for Cx patients, compared to 0.6% for placebo and 0.3% for active control patients. There was an increase in incidence of rash at higher Cx doses, with the maximal incidence of 3.4% associated with the 400 mg BID dose suggesting a dose-response relationship. Importantly, there were no serious cutaneous reactions associated with Cx treatment, including Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), or erythema multiforme. In addition, photosensitivity reactions were not associated with Cx treatment, consistent with the fact that Cx (the chemical) does not absorb light in UVA and UVB regions of the spectrum.

The mechanism of rash development associated with Cx treatment is not known, but does not appear to be allergic in nature, due to the lack of association with eosinophilia. Celecoxib does not bind to the skin or to melanin, and radiolabeled studies did not show increased cutaneous compartmentalization compared to plasma levels. However, since Cx is a sulfonamide-containing molecule, it is certainly possible, that sulfa sensitivity is the mechanism (whatever that may be) responsible for many Cx-associated cutaneous reactions. **In view of the possible etiologic link to sulfonamide sensitivity, physicians should exercise caution in prescribing CX to patients with a known history of systemic sulfa reaction.**

## Respiratory Tract Safety:

The NDA did not include any studies with end points specifically related to effects on pulmonary or respiratory function, however, AEs were analyzed.

In the NA arthritis trials, the overall incidences of events in the respiratory system were similar among treatment groups (Text Table 185, ISS, includes bronchitis, coughing, dyspnea, pharyngitis, rhinitis, sinusitis, URTI). The incidences did not consistently increase with increasing doses of Cx although there were some (such as bronchitis and coughing). The events of highest incidence (≥3% in any treatment group) were sinusitis and upper respiratory tract infection, but the incidences were very similar across treatment groups, including placebo. In the analyses involving Cx 400 mg BID, no respiratory events were statistically significantly more common for Cx than for placebo or active control. However, there was a statistically significant different between Cx (100 mg BID and 200 mg QD or BID) and placebo in the NA arthritis trials and international arthritis trials for pharyngitis and URTI (Text Table 186, ISS).

In the NA arthritis trials, very few patients in any treatment group withdrew due to an AE related to the respiratory system. The analyses of AEs causing withdrawal disclosed no statistically significant differences between Cx and placebo or active control, either for any single respiratory event or overall respiratory events combined.

In the controlled clinical trials, respiratory-related SAEs occurred in 30 patients (Text Table 187, ISS). All but one of these events occurred in NA or International arthritis trials, and the remaining one occurred in a multiple-dose surgical pain study (Study 028). In the long-term, open-label trial, SAEs occurred in 21 patients that were related to the respiratory system as noted in table 45 below:

**Table 45. Respiratory Serious Adverse Events: Long-Term Trial**

| Adverse Event | Cx dose (mg, BID) | | | |
|---|---|---|---|---|
| | 100 | 200 | 300 | 400 |
| Bronchitis | - | 1 | - | - |
| Dyspnea | - | 1 | - | - |
| Pleural effusion | 1 | - | - | - |
| Pleurisy | 1 | - | - | - |
| Pneumonia | 1 | 4 | 2 | 2 |
| Pneumonitis | - | - | 1 | - |
| Pulmonary infiltration | - | 1 | - | - |
| Resp. insufficiency | - | - | 1 | 2 |
| Sinusitis | - | 1 | - | - |
| Pulmonarycarcinoma | - | 1 | - | 1 |

From Text Table 188, ISS.

Presence of asthma had little effect upon the respiratory adverse event profile of Cx (Text Table 191, ISS). The incidences of bronchospasm and aggravated bronchospasm were similar for Cx and placebo among patients with asthma; these rates were higher than for patients without asthma, but again, the incidence rates

for Cx and placebo patients were nearly identical. The findings for history of bronchitis were similar and did not show any evidence of exacerbation of a respiratory condition with celecoxib.

The adverse events for which there was a statistically significant ($p \leq 0.05$) difference in the risk difference between patients who took aspirin (looking for URTI) amd antihistamines or decongestants (looking for dyspnea) and those who did not revealed no increased risk with Cx with these medications but increases without the medications compared to placebo (Text Tables 192 and 193, ISS). No increases in risk were seen when Cx was compared to active controls in this regard.

**In summary**, respiratory events were common in all treatment groups and occurred at similar incidence, suggesting that the high frequency simply reflected the common nature of these disorders in the general population. For the most part the respiratory complaints were mild to moderate in severity, and not felt by the Investigators to be related to treatment. The most common events were URI, rhinitis, sinusitis, and pharyngitis, with the latter two occurring somewhat more frequently among Cx patients. An important finding was that asthma and the related condition bronchitis were not apparently exacerbated by celecoxib. The overall rates of respiratory complaints, and importantly, the rates of bronchospasm and bronchospasm aggravated were also apparently not affected by Cx, suggesting that for the general asthmatic population (excluding those with aspirin-induced asthma), Cx may be used without concern about worsening of asthma.

## CNS/PNS Safety:

In the NDA, no specific clinical studies were performed to assess effects of Cx on the central or peripheral nervous systems, or to assess possible psychiatric effects of the drug. However, constitutive COX-2 expression has been demonstrated in the rodent brain. Although the function of the enzyme in this setting is unclear, these findings raise the question whether constitutive COX-2 is active in human brain and what effect selective COX-2 inhibition might have on the human central nervous system.

**In summary**, review of the data regarding central and peripheral nervous system and psychiatric AEs does not reveal a pattern suggestive of deleterious effects from Cx use. Commonly seen complaints of headache, dizziness and insomnia occurred with similar frequency in all treatment groups. From the subgroup analyses, there were no illnesses or medications that appeared to augment the frequency of adverse events. There also was no demographic subgroup for which there was an increased or disproportionate distribution of central or peripheral nervous system or psychiatric.

## Infection Disease Safety:

Because it was felt that the preclinical studies did not demonstrate any potential issues related to infections with Cx, and there are no clinically significant infectious complications of therapy with non-selective COX inhibitors (NSAIDs), the NDA did not include any studies with endpoints specifically related to infections. However, it is recognized that as a general principle, treatment with any anti-inflammatory drug may mask potential symptoms thus creating the possibility that infections could present in a more advanced state due to the suppression of early symptoms (the Preclinical review suggests there may be some increased incidences of skin infections in certain species).

Review of the NDA clinical database did not demonstrate any obvious evidence that Cx increased the risk of infections or infectious complications. Common infections were seen generally in all placebo, Cx and active control patients. The only AEs possibly infectious in nature that occurred more frequently in Cx patients (see also Respiratory Safety) were upper respiratory tract infection and pharyngitis.

Serious adverse events relating to infection with the Preferred Terms of Cellulitis, Abcess, Infection, Urinary Tract Infection, Secondary sepsis, Sepsis, or Pelvic Inflammation revealed a total of 16 SAEs in the controlled trials and 15 events in the open-label trials. Four of the 16 in the controlled portions were in patients taking Cx and there were 4 withdrawals; there were no with in the open-label trials (Text Table 203, ISS). It should be noted that none of these SAEs were considered by the Searle Safety or Medical Monitors to have been caused by the study medication. In controlled trials the incidence of infection-related SAEs between Cx and placebo was similar (9/9492 = 0.09%, 1/1345 = 0.07%, respectively) but was higher in active control patients (7/2255 = 0.31%).

**In summary**, none of the available data suggest that Cx is obviously associated with an increased risk of infection. Further, no interaction was found with any medication taken to augment the incidence of infections.

# Overall Safety:

## Adverse Events

Adverse events were coded using the World Health Organization Adverse Reaction Terminology (WHO) dictionary. Conventions for assigning Included and Preferred Terms to certain events were adopted in order to ensure consistent coding of events among different studies and coders. In addition, nine new adverse event codes were introduced to correct for ambiguities in the WHO dictionary. The new Preferred Terms were blurred vision, ecchymosis, hemorrhoids bleeding, hiatal hernia, H. pylori, infection soft tissue, neck stiffness, peripheral pain, and treatment-emergent surgery.

As noted in the 120-day Safety Update, overall, 82.8% of the open-label patients experienced at least one adverse event at the time of this Update, compared to 73.9% at the time of the ISS, and 60.5% of patients receiving celecoxib in the double-blind, placebo-controlled North American Arthritis trials. Table 46 summarizes the most common adverse events occurring in the long-term open label trial at the time of this Update, and presents the incidences of these events occurring in the long-term, open-label trial at the time of the ISS and in the double-blind, placebo-controlled North American arthritis studies for comparison.

**Table 46. Adverse Events with ≥3% Incidence: Long-Term Trial (Study 024)**

| | Adverse Event | Incidence, % | | |
|---|---|---|---|---|
| | | Long-term Open Label Trial, SU | Long-term Open Label Trial, ISS | North American Arthritis Studies* |
| | Any event | 82.8 | 73.9 | 60.5 |
| Most common events in controlled North American arthritis studies (≥3% in any celecoxib group) | Headache | 17.0 | 16.0 | 17.7 |
| | Dyspepsia | 12.0 | 10.1 | 9.9 |
| | URTI | 19.5 | 14.1 | 8.8 |
| | Diarrhea | 9.0 | 7.7 | 6.6 |
| | Sinusitis | 11.4 | 9.2 | 5.5 |
| | Abdominal pain | 7.0 | 5.5 | 5.2 |
| | Nausea | 6.5 | 5.4 | 3.7 |
| | Back pain | 5.8 | 4.3 | 3.0 |
| | Injury accidental | 9.5 | 7.2 | 3.0 |
| | Rash | 4.9 | 4.2 | 3.4 |
| Additional events occurring with a frequency of ≥3% in the long-term open label trial | Bronchitis | 5.6 | 4.2 | 2.1 |
| | Dizziness | 5.0 | 4.1 | 2.4 |
| | Edema peripheral | 5.0 | 3.8 | 2.9 |
| | Coughing | 4.6 | 3.5 | 2.1 |
| | Influenza-like symptoms | 4.4 | 2.9 | 1.8 |
| | Insomnia | 4.4 | 3.4 | 2.5 |
| | Urinary tract infection | 4.3 | 3.2 | 1.6 |
| | Rhinitis | 4.2 | 3.1 | 2.1 |
| | Tooth disorder | 4.0 | 2.9 | 1.9 |
| | Pharyngitis | 3.7 | 2.9 | 2.5 |
| | Myalgia | 3.1 | 2.5 | 2.0 |
| | Hypertension | 3.1 | 1.7 | 1.0 |

Numbers are percentages of patients.

*This column includes the highest incidence from among the 100 mg BID, 200 mg QD or BID, and 400 mg BID dose groups in ISS Table 6.2.

Similar to the ISS in the NDA, the most frequently reported adverse events were upper respiratory tract infection, headache, dyspepsia, sinusitis, and injury accidental. Adverse events occurring with an overall incidence of 3% or more as of the Update that did not occur with such frequency in the ISS are influenza-like symptoms, tooth disorder, pharyngitis, hypertension, and myalgia. Note that since patients enrolled in the long-term trial may have entered directly from a controlled arthritis trial, some adverse events may be counted in both columns. The overall incidences of adverse events are higher in the long-term open label study than in the North American arthritis studies, reflecting the fact that adverse event rates increase with increasing duration of exposure in the open-label study.

In order to better evaluate events that emerge after durations longer than the controlled studies (2 to 12 weeks), prevalence and incidence during 180-day intervals are summarized in table 47. This table summarizes events for which the incidence (new events in interval) was greater than 1% in intervals beyond the first 180-day interval. Adverse events appearing in this analysis for this Update that did not appear in a similar analysis in the ISS are chest pain, hypertension, influenza-like symptoms, insomnia, neuralgia, peripheral edema, pharyngitis, rash, synovitis, and tooth disorder. There does not appear to be an overall trend for the incidence of new adverse events with Cx increase over time.

**Table 47. Adverse Events: Incidence ≥1% (Any Interval >180 Days) in Study 024**

| | Interval | | | | |
|---|---|---|---|---|---|
| **Adverse Event** | **1-180** | **181-360** | **361-540** | **541-720** | **>720** |
| No. who entered interval | 5155 | 3980 | 2453 | 1168 | 124 |
| Headache | 15.2 | 2.3 | 0.8 | 1.1 | 0.0 |
| URTI | 13.8 | 5.7 | 4.7 | 1.2 | 0.0 |
| Dyspepsia | 9.7 | 2.4 | 1.1 | 0.6 | 0.0 |
| Sinusitis | 8.4 | 3.0 | 1.9 | 0.9 | 0.0 |
| Diarrhea | 7.2 | 1.8 | 0.9 | 0.8 | 0.0 |
| Injury accidental | 6.2 | 3.1 | 1.7 | 1.7 | 0.0 |
| Abdominal pain | 5.3 | 1.6 | 0.8 | 0.6 | 0.0 |
| Nausea | 5.0 | 1.3 | 0.9 | 0.7 | 0.0 |
| Bronchitis | 3.9 | 1.5 | 1.2 | 0.5 | 0.0 |
| Dizziness | 3.9 | 1.0 | 0.6 | 0.4 | 0.0 |
| Back pain | 3.8 | 1.9 | 1.0 | 0.9 | 0.0 |
| Rash | 3.7 | 1.0 | 0.8 | 0.4 | 0.0 |
| Peripheral edema | 3.4 | 1.3 | 1.1 | 0.6 | 0.0 |
| Coughing | 3.2 | 1.1 | 1.1 | 0.0 | 0.0 |
| Influenza-like symptoms | 3.1 | 1.0 | 1.3 | 0.0 | 0.0 |
| Insomnia | 3.1 | 1.3 | 0.8 | 0.2 | 0.0 |
| Tooth disorder | 2.6 | 1.3 | 0.8 | 0.3 | 0.0 |
| Pharyngitis | 2.5 | 1.1 | 0.8 | 0.2 | 0.0 |
| UTI | 2.5 | 1.7 | 1.1 | 0.6 | 0.0 |
| Hypertension | 1.6 | 1.2 | 1.2 | 0.2 | 0.0 |
| Neuralgia | 1.5 | 1.1 | 0.6 | 0.2 | 0.0 |
| Chest pain | 1.3 | 1.0 | 0.6 | 0.5 | 0.0 |
| Prostatic disorder* | 1.2 | 1.3 | 0.1 | 0.7 | 0.0 |
| Synovitis | 1.2 | 1.0 | 0.5 | 0.3 | 0.0 |

**All numbers are percentages of patients unless otherwise specified.**
***N for men=1550 for 1-180 days; N=1207 for 181-360 days; N=720 for 361-540 days; N=314 for 541-720 days; and N=28 for >720 days.**