3. WHO database summary

Adverse event	*Congestive heart failure*		*Hypertension*	
	count	*%*	*count*	*%*
Ketoprofen	**7**	**0.07%**	**23**	**0.24%**
Acetaminophen	0		7	0.11%
Aspirin	4	0.03%	18	0.13%
Ibuprofen	13	0.07%	64	0.34%
Naproxen	17	0.09%	60	0.30%

4. Discussion

There have been rare reports on major cardiovascular adverse events related to ketoprofen or other frequently used NSAIDs. There is no added information of concern.

III. DIGESTIVE SYSTEM

1. Present label

Incidence	*3 to 9%*	*≥1% (<3%)*	*<1%*	*<1%*
Causal relationship	*Probable*	*Probable*	*Probable*	*Unknown*
Adverse event	Dyspepsia (11%), nausea, abdominal pain, diarrhea, constipation, flatulence	Anorexia, vomiting, stomatitis.	Appetite increased, dry mouth, eructation, gastritis, rectal hemorrhage, melena, fecal occult blood, salivation, peptic ulcer, gastrointestinal perforation, hematemesis, intestinal ulceration.	Buccal necrosis, ulcerative colitis, microvesicular steatosis, jaundice, pancreatitis.

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2a. SRS database summary - major gastrointestinal complications

Adverse event	*GI hemorrhage*			*GI perforation*			*Ulcer bleeding and perforation*		
Count	*event %*	*serious %*	*death %*	*event %*	*serious %*	*death %*	*event %*	*serious %*	*death %*
Ketoprofen	**108**	**70**	**8**	**8**	**7**	**1**	**0**	**0**	**0**
	6.09%	**11.9%**	**7.77%**	**0.45%**	**1.19%**	**0.97%**			
Acetaminophen	35	31	17	2	2	2	0	0	0
	0.85%	1.32%	1.74%	0.05%	0.09%	0.20%			
Aspirin	538	391	28	8	7	0	1	1	1
	14.6%	21.1%	9.30%	0.22%	0.38%	0	0.03%	0.05%	0.33%
Ibuprofen	987	746	63	45	31	12	6	4	0
	5.83%	13.3%	8.54%	0.25%	0.52%	1.63%	0.04%	0.07%	
Naproxen	995	606	122	80	63	36	9	9	4
	6.02%	12.4%	13.9%	0.48%	1.27%	4.11%	0.05%	0.18%	0.46%
Diclofenac Na	334	244	120	58	58	48	6	6	3
	4.17%	6.89%	9.39%	0.72%	1.64%	3.76%	0.07%	0.17%	0.23%
Indomethacin	476	267	80	98	72	39	13	10	8
	7.01%	9.55%	9.14%	1.44%	2.58%	4.46%	0.19%	0.36%	0.91%
Piroxicam	964	546	118	126	102	30	21	15	3
	10.6%	17.5%	16.0%	1.38%	3.26%	4.05%	0.23%	0.48%	0.41%

(Note: Gastrointestinal hemorrhage listed in the table incudes the following COSTART terms: hemorrhagic gastritis, gastrointestinal hemorrhage, rectal hemorrhage, hematemesis, melena, duodenal ulcer hemorrhage, peptic ulcer hemorrhage, and stomach ulcer hemorrhage. Gastrointestinal perforation listed in the table incudes the following COSTART terms: gastrointestinal perforation, intestinal perforation, intestinal ulcer perforation, duodenal ulcer perforation, peptic ulcer perforation, and stomach ulcer perforation. Ulcer bleeding and perforation listed in the table incudes the following COSTART terms: duodenal ulcer bleeding

and perforation, peptic ulcer bleeding and perforation, and stomach ulcer bleeding and perforation.)

3a. WHO database summary - major gastrointestinal complications

Adverse event	*GI hemorrhage*		*GI perforation*		*Ulcer bleeding and perforation*	
	count	*%*	*count*	*%*	*count*	*%*
Ketoprofen	**951**	**9.89%**	**18**	**0.19%**	**0**	
Acetaminophen	88	1.32%	7	0.11%	1	0.02%
Aspirin	2688	19.68%	49	0.36%	8	0.07%
Ibuprofen	1353	7.18%	111	0.59%	6	0.03%
Naproxen	1944	9.81%	156	0.79%	6	0.03%
Diclofenac Na	1547	7.50%	220	1.07%	10	0.05%
Indomethacin	1620	8.87%	360	1.97%	14	0.08%
Piroxicam	2541	13.8%	411	2.24%	13	0.07%

(Note: The WHOART terms are grouped in a similar way as mentioned above.)

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2b. SRS database summary - major liver toxicities

Adverse event	*Liver failure*			*Liver necrosis*			*Liver damage*		
Count	*event %*	*serious %*	*death %*	*event %*	*serious %*	*death %*	*event %*	*serious %*	*death %*
Ketoprofen	**1**	**1**	**1**	**0**	**0**	**0**	**1**	**1**	**0**
	0.06%	**0.17%**	**0.97%**				**0.06%**	**0.17%**	
Acetaminophen	92	89	60	107	93	69	76	60	13
	2.24%	3.80%	6.13%	2.61%	3.97%	7.06%	1.85%	2.56%	1.92%
Aspirin	1	1	1	2	1	1	6	4	2
	0.03%	0.05%	0.33%	0.05%	0.05%	0.33%	0.16%	0.22%	0.66%
Ibuprofen	3	3	3	11	8	5	7	4	2
	0.02%	0.05%	0.41%	0.06%	0.14%	0.68%	0.04%	0.07%	0.27%
Naproxen	9	6	5	20	19	17	18	10	1
	0.05%	0.12%	0.57%	0.12%	0.39%	1.94%	0.11%	0.20%	0.11

3b. WHO database summary - major liver toxicities

Adverse event	*Liver failure*		*Liver necrosis*		*Liver damage*	
	count	*%*	*count*	*%*	*count*	*%*
Ketoprofen	**2**	**0.02%**	**0**		**6**	**0.06%**
Acetaminophen	58	0.87%	58	0.87%	27	0.41%
Aspirin	7	0.05%	1	0.01%	11	0.08%
Ibuprofen	4	0.02%	9	0.05%	10	0.05%
Naproxen	7	0.04%	14	0.07%	19	0.10%

2c. SRS database summary - major liver toxicities (cont.)

Adverse event	*Cholestatic hepatitis*			*Jaundice*		
Count	*event %*	*serious %*	*death %*	*event %*	*serious %*	*death %*
Ketoprofen	**6**	**5**	**1**	**11**	**8**	**1**
	0.34%	**0.85%**	**0.97%**	**0.62%**	**1.36%**	**0.97%**
Acetaminophen	5	5	1	30	25	11
	0.12%	0.21%	0.10%	0.73%	1.07%	1.12%
Aspirin	5	2	1	10	6	3
	0.14%	0.11%	0.33%	0.27%	0.32%	1.00%
Ibuprofen	24	7	0	56	16	4
	0.14%	0.12%		0.33%	0.29%	0.54%
Naproxen	26	6	1	65	17	3
	0.16%	0.12%	0.11%	0.39%	0.35%	0.34%

(Note: The COSTART term for cholestatic hepatitis is cholestatic jaundice.)

3c. WHO database summary - major liver toxicities (cont.)

Adverse event	*Cholestatic hepatitis*		*Jaundice*	
	count	*%*	*count*	*%*
Ketoprofen	**18**	**0.19%**	**18**	**0.19%**
Acetaminophen	37	0.56%	84	1.26%
Aspirin	22	0.16%	52	0.38%
Ibuprofen	44	0.23%	90	0.48%
Naproxen	44	0.22%	114	0.58%

4. Discussion

a. Major gastrointestinal complications

As stated in the current labels:" Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time with or without warning symptoms, in patients treated chronically with NSAID therapy...In patients observed in clinical trials of several months to two years' duration, symptomatic upper-GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2-4% patients treated for one year." Serious gastrointestinal complication is a major safety concern for patients on higher doses and longer exposure of NSAIDs.

The counts and percentages of gastrointestinal bleeding, perforation, and ulcer bleeding and perforation are summarized in the tables on previous pages. In SRS database summary, aspirin and piroxicam have a higher reporting frequency of serious GI hemorrhage; piroxicam and naproxen have a higher reporting frequency of death due to GI hemorrhage. Keep in mind these figures can not be used as basis for comparison as stated before.

There have been many attempts to estimate the magnitude of the risk of major GI complications associated with an individual NSAID and the relative risk among different NSAIDs. The findings from the epidemiological studies vary and are very difficult to interpret. A request for consultation with regard to 7 recent articles on relative toxicity of NSAIDs was sent to the Division of Epidemiology and Surveillance. Four of these are epidemiological studies with a case-control design that evaluate the major GI complications associated with various NSAIDs published since 1993 and are selected for discussion here (see Appendix C4 for References).

(1). Langman MJS, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RFA, Murphy M, Vessey MP, Colin-Jones DG. **Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs.** Lancet 1994;343:1075-1078.

Summary: This is a case-control study carried out in the United Kingdom. Cases (n=1144) were ascertained as patients age 60 or over, hospitalized with UGI bleed (endoscopy or surgical confirmation). There were two sets of controls, matched by sex and by age within 5 years, one set (n=1126) from hospitalized patients and the other set (n=989) from the outpatient physician's register. Exposure was ascertained by questionnaire, supplemented by information from hospital and physician records. Odds ratios were calculated for each of seven non-aspirin NSAIDs (azapropazone, ketoprofen, piroxicam, indomethacin, naproxen, diclofenac, and ibuprofen), by unconditional logistic regression with the two control groups combined, using no NSAID or aspirin exposure history as the reference category. The odds ratio for ulcer complications associated with ketoprofen was 23.7 (95% confidence interval 7.6-74.2), higher than for any other NSAID except azapropazone. Dose categories were defined based on the recommendations of British National Formulary as the following:

	Low dose	*Medium dose*	*High dose*
Azapropazone	<600 (mg/day)	600-899 (mg/day)	≥900 (mg/day)
Ketoprofen	**<100 (mg/day)**	**100-199 (mg/day)**	**≥200 (mg/day)**
Piroxicam	<10 (mg/day)	20 (mg/day)	≥30 (mg/day)
Indomethacin and diclofenac	<75 (mg/day)	75-149 (mg/day)	≥150 (mg/day)
Naproxen	<500 (mg/day)	500-999 (mg/day)	≥1000 (mg/day)
Ibuprofen	<1200 (mg/day)	1200-1799 (mg/day)	≥1800 (mg/day)

Risks of ulcer complications increased with advancing dose in general. Dose-response was not examined for individual NSAID. The risk for azapropazone was especially associated with the treatment of gout, but no differential risk with respect to treatment indication was detected for ketoprofen, indomethacin, or NSAIDs in general.

Comment: The unmatched analysis of a matched design could lead to underestimates of exposure odds ratios (bias toward the null). It could alter the relationships between odds ratios for different drugs if the age and sex distribution for ketoprofen differed from those for other NSAIDs. This effect should be mitigated by the fact that all patients were drawn from a restricted age range, and the authors state that "age and sex were not found to be confounders." Recall bias and the use of medical record information for hospitalized patients could lead to more complete ascertainment of drug exposure for cases than controls, but there is no reason to suppose this would affect the comparison between different NSAIDs. There were few users of ketoprofen (31 cases and 6 controls), leading to unstable risk estimates, but even the lower bound of the 95% confidence interval is quite high (7.6), and the 95% confidence interval for ketoprofen does not overlap the confidence intervals for the two drugs with lowest odds ratios. Overall, this study does suggest a higher risk associated with ketoprofen than with most of the other NSAIDs examined, including naproxen and ibuprofen.

(2). Garcia Rodriguez LA, Jick H. **Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs.** Lancet 1994;343:769-772.

Summary: This is a case-control study carried out in the VAMP database of general-practitioner records in the United Kingdom. Cases (n=862) were identified by diagnostic codes for upper GI bleed. Controls (n=9017) were selected randomly from the same practices. Exposure was determined from prescription records. Odds ratio for upper GI bleeding and perforation associated with ketoprofen current use was 5.4 fourth out of seven individual NSAIDs (azapropazone, piroxicam, indomethacin, ketoprofen, diclofenac, naproxen, and ibuprofen) examined, and was higher than naproxen and ibuprofen

Comments: There were few ketoprofen users (14 cases and 20 controls), so that dose-response could not be assessed for this drug. There did appear to be a dose effect for two of the more commonly used NSAIDs (ibuprofen and indomethacin), but not for two others (naproxen and diclofenac) with enough use to derive an estimate. Interactions were found between NSAID use and age and ulcer history, but these were not examined for individual drugs.

(3). Henry D, Dobson A, Turner C. **Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs.** Gastroenterology 1993;105:1078-1088.

Summary: This is a case-control study carried out in New South Wales, Australia. Cases were ascertained as patients admitted to three public hospitals with upper GI bleeding that was confirmed at endoscopy or surgery or considered to be documented by "firm evidence" historically. Controls were sex and age matched either from hospital medical admissions or from physicians' practice lists. The study was conducted in two phases: the first with only subjects age 60 or over and controls from both hospital and community populations; the second with no age restrictions and controls from the hospital only. The authors state that preliminary data analysis showed very similar results for the two phases, and thus data were combined for further analysis. Drug exposure was ascertained by interview with backup information from physicians' records. Total amount of drug consumed in previous week was converted to the number of standard dose units based on the minimum daily dose recommended for rheumatoid arthritis by the manufacturers. The duration of use was expressed in terms of starting treatment within or before the previous 4 weeks. Odds ratios for exposure to individual NSAIDs were determined using conditional logistic regression (matched analysis). Differential risk with respect to treatment indication was not examined. The odds ratio for upper GI complications associated with ketoprofen was 3.6 the second highest of 8 NSAIDs (diflunisal, ketoprofen, indomethacin, naproxen, piroxicam, sulindac, diclofenac, and ibuprofen) examined. Ketoprofen also had the second highest average dosage (the number of standard dose units) consumed by case patients who used the drug. A dose-response was seen for aggregate dose units but not examined for individual drugs; rank order of different drugs was related to half life (Spearman correlation coefficient 0.643) more strongly than to average dose (coefficient 0.333).

Comment: The use of predominantly hospitalized controls, and the use of interviews as the principal measurement of exposure, could each lead to biased estimates of exposure odds ratios, but there is no evident reason why such mis-estimation should differ between NSAIDs. This study included esophageal as well as gastric and duodenal bleeding, while esophageal lesions were specifically excluded from at least one other study. Bleeding from esophageal lesions was not associated with the use of non-aspirin NSAID as a class, but increased two times with the use of aspirin according to the author. Such risk was not examined for specific NSAIDs. The dosing frequency was not used as covariate, but could be one of the contributing factors to the risk of GI complications. Patients without a past history of peptic ulcer had higher odds ratio for UGI complications associated with the use of NSAIDs than those who had peptic ulcer in the past (probably due to the warnings against NSAID uptake in these patients), but the relationship

between disease status and GI complications of individual NSAIDs was not provided in the article.

(4). Savage RL, Moller PW, Ballantyne CL, Wells JE. **Variation in the risk of peptic ulcer complications with nonsteroidal antiinflammatory drug therapy.** Arthritis and Rheumatism 1993;36:84-90.

Summary: This is a case-control study conducted in Christchurch, New Zealand. Cases (494) were ascertained by hospitalization with GI bleeding or possible perforation, with ulcers (or gastritis or erosions, analyzed separately) identified at endoscopy, surgery, or necropsy. Controls (972) were sex and age matched from other acute admissions. Exposure was ascertained by interview with supplemental information from medical records. Odds ratios were calculated on matched data. Odds ratio for the risk of perforation and hemorrhage of peptic ulcer associated with ketoprofen exposure ranged from depending on covariate adjustments; the adjusted odds ratio was 2.4 the second lowest of 7 NSAIDs (indomethacin, piroxicam, naproxen, sulindac, diclofenac, ketoprofen, and ibuprofen) examined. There were 21 cases and 16 controls with ketoprofen exposure.

Comment: In this study, ketoprofen ranked between naproxen and ibuprofen, with substantial overlap in confidence intervals. This study used only inpatient controls, so comparability with the general population is uncertain (although references are cited to support a similar distribution of NSAID use in hospitalized and non-hospitalized populations).

CONCLUSIONS

In these four studies, ketoprofen generally ranked in the mid- to high-risk category as compared to other NSAIDs for association with GI toxicity. Possible weaknesses in this assessment include:

(a). All 4 studies were foreign studies. The population risk factors (genetic and behavioral) could differ from what would be expected in the US.

(b). In these studies reflecting recent usage patterns of different drugs, one cannot definitely determine which reported differences between NSAIDs are due to intrinsic differences in toxicity and which are due to differences in the way they are typically used in practice. For example, it has been suggested that low toxicity of ibuprofen in some studies is partly due to its low-dose, short-duration use for minor musculoskeletal complaints.

Dose-response and duration effects could not be assessed for ketoprofen because of the relatively small number of users of this drug in any one study. There appeared to be an aggregate dose-response effect for all drugs combined in several studies, but it is unclear whether this would hold for each individual drug, or what the threshold dose would be for increased risk with a given drug. Two studies which looked at average doses used provided conflicting information on whether usual usage of ketoprofen is at a high dose relative to usual usage of other NSAIDs.

(c). If there are systematic differences in the type of patient for whom ketoprofen is prescribed that were not detected by the adjustment for confounders in the case-control studies, estimates of risk could be systematically biased. However, these studies provide no definite hypothesis for such an unmeasured confounder, and the small number of ketoprofen users makes it difficult to predict what risk patterns would arise in a larger population.

Overall, these studies using a variety of methods, patient populations, and outcome measures suggest that ketoprofen as it has been used in recent years is associated with somewhat more GI toxicity than a number of other NSAIDs. They do not provide adequate information to predict whether this would be the case for ketoprofen used at lower doses, for shorter durations, or in different population groups.

b. Liver toxicity

Acute liver toxicities have been associated with NSAIDs in general. They occur much less frequently with NSAIDs than with acetaminophen. One case of acute hepatitis, reported to FDA in 1994, was probably related to ketoprofen. The patient had negative viral titers, positive dechallenge with ketoprofen (rechallenge was not performed), concomitant drugs not known to cause hepatotoxicities, and other etiological factors all excluded.

IV. ENDOCRINE SYSTEM

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event				Diabetes mellitus (aggravated)

2. Discussion

There have been rare reports on endocrine adverse events related to ketoprofen or other frequently used NSAIDs. There is no added information of safety concern.

V. HEMIC AND LYMPHATIC SYSTEM

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event			Hypocoagulability, agranulocytosis, anemia, hemolysis, purpura, thrombocytopenia.	

2. SRS database summary

Adverse event	***Agranulocytosis***			***Aplastic anemia***		
Count	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***
Ketoprofen	**2**	**1**	**1**	**3**	**3**	**3**
	0.11%	**0.17%**	**0.97%**	**0.17%**	**0.51%**	**2.91%**
Acetaminophen	6	3	2	3	3	3
	0.15%	0.13%	0.20%	0.07%	0.13%	0.31%
Aspirin	5	3	3	2	2	1
	0.14%	0.16%	1.00%	0.05%	0.11%	0.33%
Ibuprofen	17	8	3	24	12	7
	0.10%	0.14%	0.41%	0.14%	0.21%	0.95%
Naproxen	32	16	7	44	33	20
	0.19%	0.33%	0.80%	0.27%	0.67%	2.29%

3. WHO database summary

Adverse event	*Agranulocytosis*		*Aplastic anemia*	
	count	*%*	*count*	*%*
Ketoprofen	**12**	**0.12%**	**6**	**0.06%**
Acetaminophen	67	1.01%	10	0.15%
Aspirin	55	0.40%	18	0.13%
Ibuprofen	71	0.38%	46	0.24%
Naproxen	61	0.31%	62	0.31%

4. Discussion

Agranulocytosis and aplastic anemia have been reported to be associated with NSAIDs and are mentioned here because of their serious outcomes. There was a report of death in a patient who developed thrombocytopenic purpura, agranulocytosis, and aplastic anemia after 69 days of Orudis and died of sepsis. Ketoprofen could not be ruled out along with aspirin as probable causes of these hematological reactions.

VI. METABOLIC AND NUTRITIONAL DISORDERS

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event			Thirst, weight gain, weight loss, hepatic dysfunction, hyponatremia.	

2. Discussion

Hepatic injury is discussed in digestive system section. There are no major metabolic and nutritional adverse reactions or added information of safety concerns for ketoprofen.

VII. MUSCULOSKELETAL SYSTEM

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event			Myalgia.	

2. Discussion

There are no reports of major musculoskeletal toxicity associated with ketoprofen or added information of safety concern.

VIII. NERVOUS SYSTEM

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event	Headache, CNS inhibition (i.e., pooled reports of somnolence, malaise, depression, etc.) or excitation (i.e., insomnia, nervousness, dreams, etc.)	Dizziness.	Amnesia, confusion, impotence, migraine, paresthesia, vertigo.	Dysphoria, hallucination, libido disturbance, nightmares, personality disorder, aseptic meningitis.

2. SRS database summary

Adverse event	***Meningitis***			***Convulsions***		
Count	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***
Ketoprofen	**2**	**2**	**0**	**5**	**1**	**0**
	0.11%	**0.34%**		**0.28%**	**0.17%**	
Acetaminophen	0	0	0	39	27	14
				0.95%	1.15%	1.43%
Aspirin	2	2	0	10	5	3
	0.05%	0.11%		0.27%	0.27%	1.00%
Ibuprofen	96	64	3	85	44	4
	0.57%	1.14%	0.41%	0.50%	0.78%	0.54%
Naproxen	21	17	3	59	29	4
	0.13%	0.35%	0.34%	0.36%	0.59%	0.46%

(Note: Aseptic meningitis is not listed as a COSTART term.)

3. Who database summary

Adverse event	*Meningitis*		*Convulsions*	
	count	*%*	*count*	*%*
Ketoprofen	**1**	**0.01%**	**11**	**0.11%**
Acetaminophen	1	0.02%	19	0.29%
Aspirin	0		22	0.16%
Ibuprofen	81	0.43%	63	0.33%
Naproxen	17	0.09%	35	0.18%

(Note: Aseptic meningitis is not listed as a WHOART term.)

4. Discussion

Rare cases of aseptic meningitis have been reported in patients using NSAIDs in general. One was a 1991 literature report in Argentina on a patient who developed concurrent episodes of aseptic meningitis and Stevens Johnson Syndrome after 5 days treatment of ketoprofen suppositories.

IX. RESPIRATORY SYSTEM

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event			Dyspnea, hemoptysis, epistaxis, pharyngitis, rhinitis, bronchospasm, laryngeal edema.	

2. SRS database summary

Adverse event	***Asthma***			***Dyspnea***			***Laryngeal edema***		
Count	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***
Ketoprofen	**17**	**10**	**0**	**29**	**9**	**0**	**3**	**2**	**0**
	0.96%	**1.69%**		**1.63%**	**1.53%**		**0.17%**	**0.34%**	
Acetaminophen	12	5	0	30	13	3	3	1	0
	0.29%	0.21%		0.73%	0.55%	0.31%	0.07%	0.47%	
Aspirin	24	8	1	41	22	3	3	2	0
	0.65%	0.43%	0.33%	1.11%	1.18%	1.00%	0.08%	0.11%	
Ibuprofen	102	37	6	217	87	8	22	12	1
	0.60%	0.66%	0.81%	1.28%	1.55%	1.08%	0.13%	0.21%	0.14%
Naproxen	121	49	9	382	120	14	26	8	1
	0.73%	1.00%	1.03%	2.31%	2.45%	1.60%	0.16%	0.16%	0.11%

3. WHO database summary

Adverse event	*Asthma*		*Dyspnea*		*Laryngeal edema*	
	count	*%*	*count*	*%*	*count*	*%*
Ketoprofen	**84**	**0.87%**	**85**	**0.88%**	**9**	**0.09%**
Acetaminophen	47	0.71%	47	1.46%	97	0.20%
Aspirin	204	1.49%	204	1.56%	213	0.32%
Ibuprofen	305	1.62%	305	1.14%	214	0.13%
Naproxen	224	1.13%	281	1.42%	27	0.14%

4. Discussion

The noticeable adverse reactions here are mostly allergic type reactions and are discussed in the section under body-as-a-whole.

X. SKIN AND APPENDAGES

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event		Rash.	Alopecia, eczema, pruritus, purpuric rash, sweating, urticaria, bullous rash, exfoliative dermatitis, photosensitivity, skin discoloration, onycholysis.	

2. SRS database summary

Adverse event	***Stevens Johnson Syndrome***			***Erythema multiforme***			***Toxic epidermal necrolysis***		
Count	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***
Ketoprofen	**5**	**1**	**0**	**3**	**2**	**1**	**1**	**0**	**0**
	0.28%	**0.17%**		**0.17%**	**0.34%**	**0.97%**	**0.06%**		
Acetaminophen	2	2	1	3	0	0	3	3	0
	0.05%	0.09%	0.10%	0.07%			0.07%	0.13%	
Aspirin	7	5	1	5	1	0	3	3	1
	0.19%	0.27%	0.33%	0.14%	0.05%		0.08%	0.16%	0.33%
Ibuprofen	34	18	5	16	5	0	14	9	4
	0.20%	0.32%	0.68%	0.09%	0.09%		0.08%	0.16%	0.54%
Naproxen	20	13	1	23	6	0	10	8	4
	0.12%	0.27%	0.11%	0.14%	0.12%		0.06%	0.16%	0.46%

3. WHO database summary

Adverse event	*Stevens Johnson Syndrome*		*Erythema multiforme*		*Toxic epidermal necrolysis*	
	count	*%*	*count*	*%*	*count*	*%*
Ketoprofen	**12**	**0.12%**	**18**	**0.19%**	**11**	**0.11%**
Acetaminophen	47	0.71%	31	0.47%	26	0.39%
Aspirin	55	0.40%	47	0.34%	20	0.15%
Ibuprofen	38	0.20%	57	0.30%	18	0.10%
Naproxen	35	0.18%	62	0.31%	19	0.10%

4. Discussion

Rare cases of serious skin disease have been reported to be associated with NSAIDs in general, including patients using ketoprofen.

APPEARS THIS WAY
ON ORIGINAL

XI. SPECIAL SENSES

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event		Tinnitus, visual disturbance	Conjunctivitis, conjunctivitis sicca, eye pain, hearing impairment, retinal hemorrhage and pigmentation change, taste perversion.	

2. Discussion

There is no added information of concern.

XII. UROGENITAL SYSTEM

1. Present label

Incidence	3 to 9%	≥1% (<3%)	<1%	<1%
Causal relationship	Probable	Probable	Probable	Unknown
Adverse event	Impairment of renal function (edema, increased BUN)	Signs or symptoms of urinary tract irritation.	Menometrorrhagia, hematuria, renal failure, interstitial nephritis, nephrotic syndrome.	Acute tubulopathy, gynecomastia.

2. SRS database summary

Adverse event	***Nephritis***			***Nephrosis***			***Acute renal failure***		
Count	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***
Ketoprofen	**3**	**2**	**0**	**3**	**3**	**0**	**10**	**9**	**3**
	0.17%	**0.34**		**0.17%**	**0.51%**		**0.56%**	**1.53%**	**2.91%**
Acetaminophen	3	2	0	0	0	0	41	36	9
	0.07%	0.09%					1.00%	1.54%	0.92%
Aspirin	8	3	0	1	1	0	12	9	3
	0.22%	0.16%		0.03%	0.05%		0.32%	0.48%	1.00%
Ibuprofen	61	38	1	33	24	2	133	94	19
	0.36%	0.68%	1.14%	0.19%	0.43%	0.27%	0.79%	1.68%	2.57%
Naproxen	55	32	6	26	14	1	77	58	15
	0.33%	0.65%	0.69%	0.16%	0.29%	0.11%	0.47%	1.18%	1.71%

3. WHO database summary

Adverse event	*Nephritis*		*Nephrosis*		*Acute renal failure*	
	count	*%*	*count*	*%*	*count*	*%*
Ketoprofen	**12**	**0.12%**	**12**	**0.12%**	**53**	**0.55%**
Acetaminophen	11	0.17%	1	0.02%	40	0.60%
Aspirin	12	0.09%	3	0.02%	39	0.29%
Ibuprofen	56	0.30%	24	0.13%	135	0.72%
Naproxen	60	0.30%	33	0.17%	98	0.49%

4. Discussion

A number of pathophysiological effects of NSAIDs on renal functions have been described in the literature, for example, reduction in glomerular filtration rate with azotemia and interstitial nephritis with nephrosis. Patients with conditions that predispose them to hypovolemia, impaired renal perfusion, or impaired renal function are especially prone to NSAID induced renal injury.

OVERDOSE

1. Present label

Signs and symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Respiratory depression, coma, or convulsions have occurred following large ketoprofen overdoses. Gastrointestinal bleeding, hypotension, hypertension, or acute renal failure may occur, but are rare.

2. SRS database summary

Adverse event	***Overdose***			***Intentional overdose***		
Count	***event %***	***serious %***	***death %***	***event %***	***serious %***	***death %***
Ketoprofen	**10**	**1**	**0**	**3**	**3**	**1**
	0.56%	**0.17%**		**0.17%**	**0.51%**	**0.97**
Acetaminophen	281	218	115	461	155	78
	6.85%	9.30%	11.8%	0.95%	1.15%	1.43%
Aspirin	41	27	9	60	37	18
	1.11%	1.45%	2.99%	1.62%	1.99%	5.98%
Ibuprofen	166	73	13	119	90	16
	0.98%	1.30%	1.76%	0.50%	0.78%	0.54%
Naproxen	131	18	6	47	12	1
	0.79%	0.37%	0.69%	0.28%	0.25%	0.11%

(Note: Overdose in the table refers to COSTART terms over dose and accidental overdose.)

3. Who database summary

Adverse event	*Overdose*		*Intentional overdose*	
	count	*%*	*count*	*%*
Ketoprofen	**5**	**0.05%**	**0**	
Acetaminophen	30	0.45%	86	1.29%
Aspirin	13	0.10%	13	0.10%
Ibuprofen	16	0.08%	41	0.22%
Naproxen	11	0.06%	12	0.06%

(Note: Overdose refers to the WHOART term increased therapeutic response; and intentional overdose refers to suicide attempt.)

4. Discussion

NSAIDs do not seem to be a drug class with great potential for committing suicide. There was only one report of fatal case from suicide. The detailed information was not available to assess the relationship between the event and Oruvail.

C. OVERALL SAFETY CONCLUSION

Many adverse reactions commonly known for the NSAID class are already listed in the current prescription labels for ketoprofen. The most frequently reported adverse reactions for ketoprofen are gastrointestinal and hypersensitive reactions. Other reactions such as renal, hepatic, hematological, and dermatological toxicity are relatively rare. The safety profile of ketoprofen is similar to ibuprofen, naproxen, and other currently available OTC analgesics in general. There may be some differences in terms of specific drug reactions, but the magnitude of the relative risk between different NSAIDs could not be adequately determined due to the limitations associated with available data. The safety data presented in this review should not be used as basis for conclusion on specific toxicity related to individual NSAIDs.

For ketoprofen 12.5 to 25mg per dose, not to exceed a daily dose of 75mg for 10 days, the adverse reactions to be expected are mostly allergic type reactions and minor gastrointestinal complains. The non-compliance rate to dosing instructions may approach 50% and will probably not lead to any increase in drug toxicities as demonstrated in actual-use study. On the whole, ketoprofen 12.5mg to be taken as instructed is considered reasonably safe for use OTC.

VI. APPENDIX

APPENDIX

A. Efficacy review appendix

1. Abbreviation and definition
2. Analgesic duration
3. Temperature variables

B. Actual-use study appendix

1. Non-compliance to dosing instruction
2. Adverse events and non-compliance

C. Safety review appendix

1. Adverse event summary - part I
2. Adverse event summary - part II
3. Drop-outs due to adverse events
4. Epidemiological studies (see next page for references below)

References

1. Langman MJS, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RFA, Murphy M, Vessey MP, Colin-Jones DG. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:1075-1078.

2. Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:769-772.

3. Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. Gastroenterology 1993;105:1078-1088.

4. Savage RL, Moller PW, Ballantyne CL, Wells JE. Variation in the risk of peptic ulcer complications with nonsteroidal antiinflammatory drug therapy. Arthritis and Rheumatism 1993;36:84-90.

APPENDIX A1

THE **ABBREVIATION**, DEFINITION, AND EXPLANATION OF COMMON ITEMS

1. DRUG NAME

APAP = acetaminophen
Ibu = ibuprofen
Nap = naproxen
ASA = Aspirin
Keto = ketoprofen
PLA = placebo

2. EFFICACY PARAMETER

PR = Pain Relief, measured on a 5-point categorical scale (**5-pt categ**), where
0 = no relief
1 = a little relief
2 = some relief
3 = a lot of relief
4 = complete relief

PI = Pain Intensity, measured on a 4-point categorical scale (**4-pt categ**), where
0 = none
1 = mild
2 = moderate
3 = severe

PID = Pain Intensity Difference, or the difference between PI at baseline and PI at each scheduled time point.

PRID = the summation of PR and PID.

Analgesic onset (or the onset of perceptible relief from the pain) was estimated as the time it takes after dosing for a treatment group to get a group mean PRID rating of 1 based on the group mean PRID at 30 minutes.

Time to remedication was defined as the time interval between the intake of study medication and the intake of rescue medication or a second dose of study medication. Pain measurements recorded after remedication were not considered valid for efficacy analysis.

Analgesic duration (or the duration of adequate relief from the pain) was estimated as the time after dosing when half of the patients in a treatment group remedicated.

3. DATA MANAGEMENT IN THE EFFICACY ANALYSIS

Time points for efficacy assessments were the time points scheduled for periodic scoring of pain intensity and pain relief.

A time window was defined as the time interval constructed around a scheduled time point to account for variability in the time of data recording. The window sizes chosen were ±5 minutes if the scheduled time separation of data recording was <1 hour and ±10 minutes if the time separation was ≥1 hour.

Missing data occurred when pain scores were not recorded in the time interval defined by the midpoints from the scheduled time point of interest to each of the surrounding time points. For example, when pain was measured at 30, 60 and 120 minutes, the 60-minute data would be considered missing if there were no pain scores in between 45 and 90 minutes.

Deviated data occurred when pain scores were recorded outside the time window but inside the time interval defined by the midpoints from the scheduled time point of interest to each of the surrounding time points.

Patients were excluded from PRID analysis if their PR, PI or both were excluded for the reason of having 2 consecutive, interpolated data points derived from the same two actual measurements in the interval of ≤2 hours, or 3 data points missing in the interval of >2 hours.

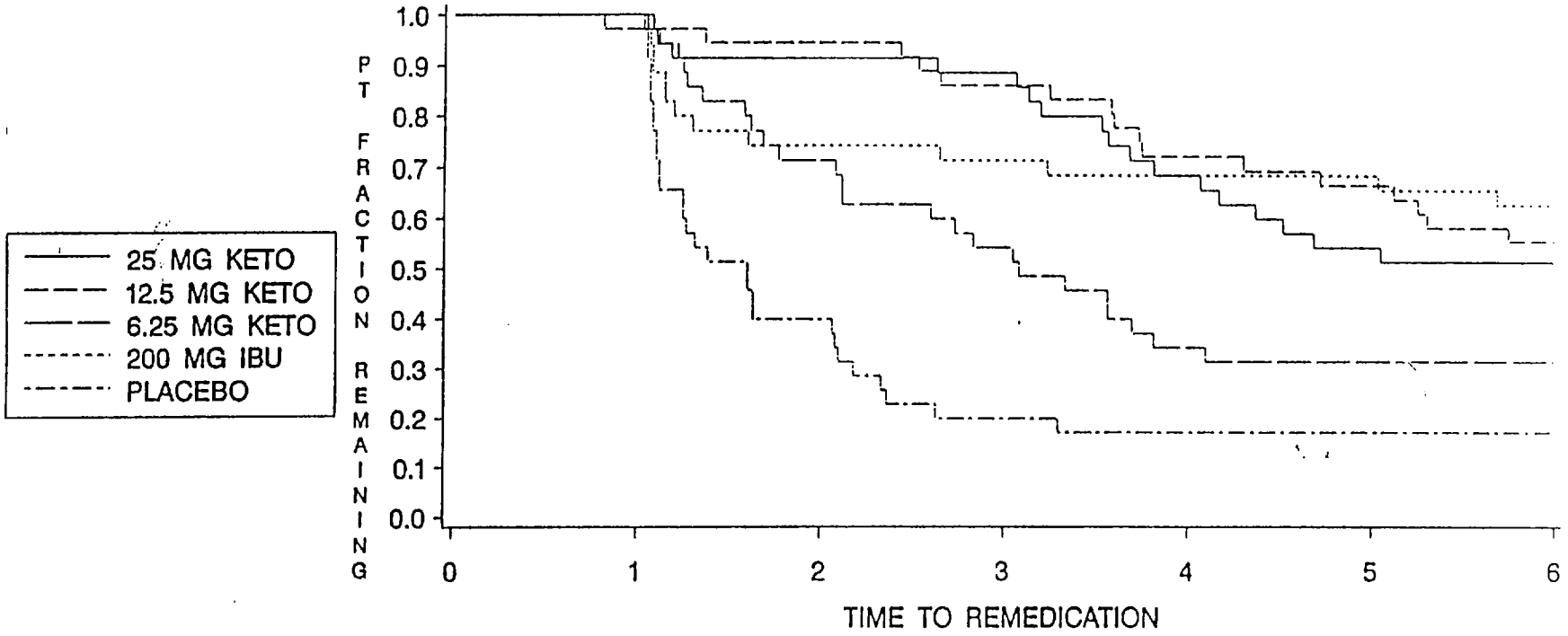
For patients who had missing or deviated data but did not meet the exclusion criteria as stated above, the pain scores were linearly interpolated from the two measured pain scores, one measured immediately before and one immediately after the scheduled time point, or extrapolated from the worst of the baseline score and last recorded score if the missing or deviated data were at the tail end of the observation period or immediately before remedication. Pain scores for the scheduled time points after remedication were extrapolated the same way and were not classified as missing data.

4. STATISTICAL SIGNIFICANCE AND PAIRWISE COMPARISONS

The means were expressed as raw means unless otherwise indicated as LS means. All the pairwise comparisons were based on the LS means. If the overall treatment p-value was less than or equal to 0.05, then the results of pairwise comparison were considered statistically significant when the p-values for the individual pairwise comparisons were also less than or equal to 0.05. The outcomes of the pairwise comparison were denoted by upper case letters, where letter A stands for the most effective treatment(s), B for the next most effective treatment, and so forth. If the overall treatment p-value was >0.05, the separation of means by unprotected pairwise t-tests would be indicated by lower case letters and was not interpreted as being statistically significant.

KETOPROFEN (BAY A 7790)/DENTAL
PROTOCOL NO: S90-002

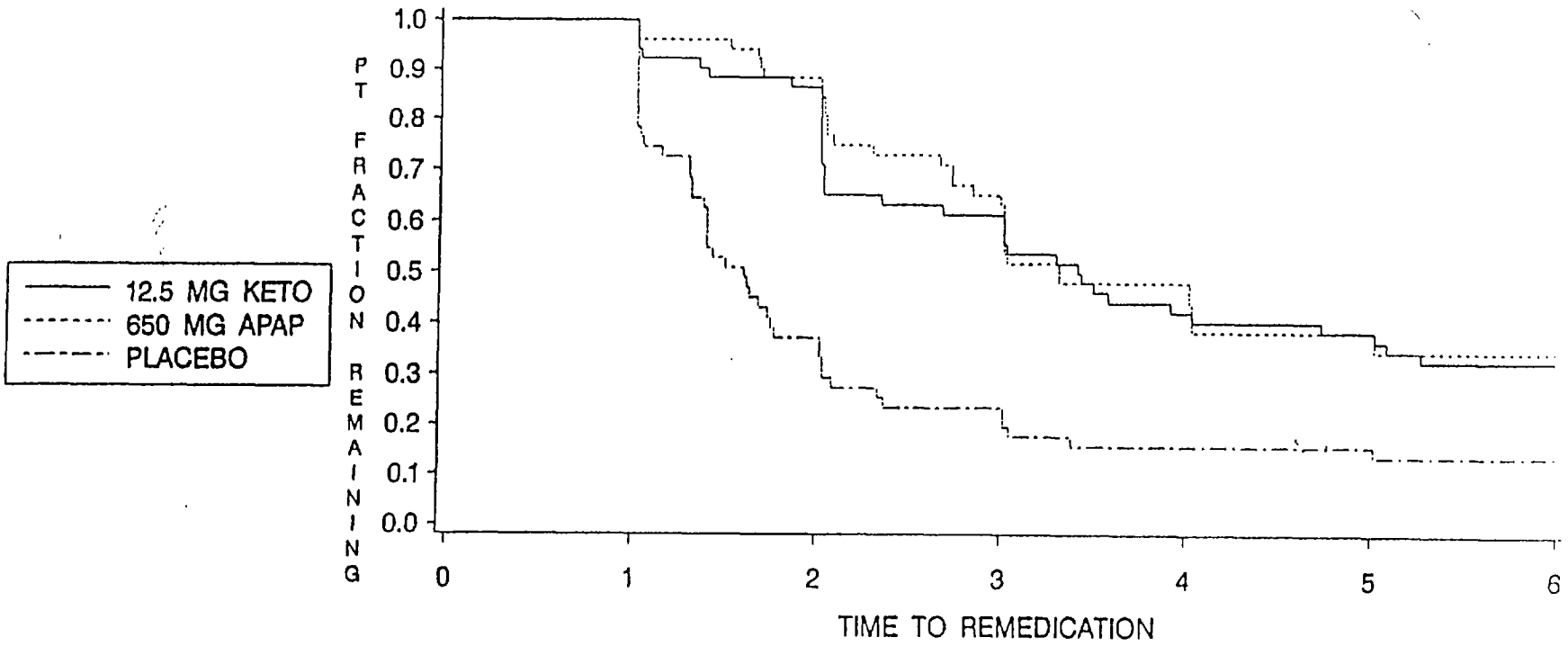
ESTIMATED DURATION OF ANALGESIA (TIME-TO-REMEDICATION)
PRODUCT LIMIT PLOT OF TIME TO REMEDICATION
FOR PATIENTS VALID FOR FDA DURATION OF ANALGESIA



Treatment	Calculated Time-to-Remedication		Tests[3]	
	Median Time (h:min)[1]	95% CI (h:min)[2]	Wilcoxon	Log Rank
Ketoprofen 25 mg	> 6:00	4:10, > 6:00	A	A
Ketoprofen 12.5 mg	> 6:00	5:07, > 6:00	A	A
Ketoprofen 6.25 mg	3:05	2:05, 3:42	B	B
Ibuprofen 200 mg	> 6:00	5:02, > 6:00	AB	A
Placebo	1:36	1:07, 2:06	C	C

[1]Kaplan-Meier estimate
[2]Method of Simon and Lee, Cancer Treat Rep 66:37 - 42, 1982
[3]Wilcoxon and Log Rank test applied as in Fisher's PLSD

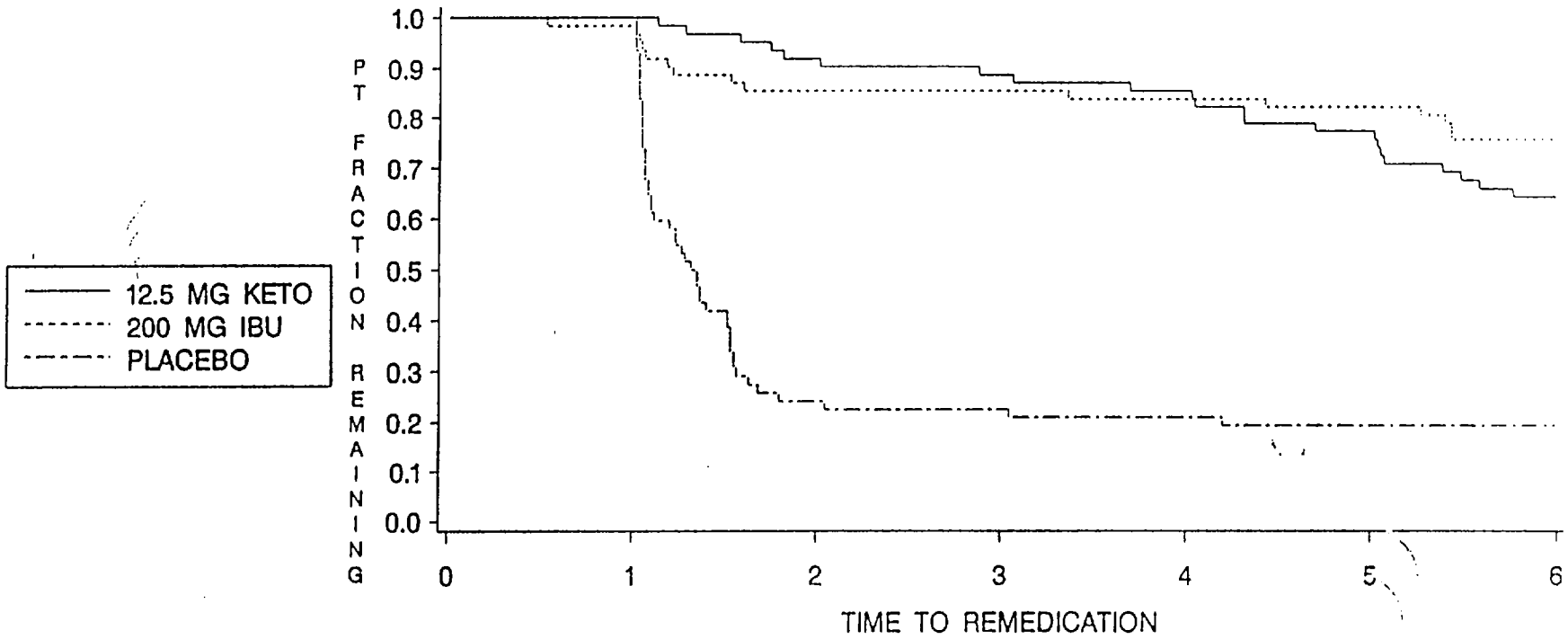
ESTIMATED DURATION OF ANALGESIA (TIME-TO-REMEDICATION)
PRODUCT LIMIT PLOT OF TIME TO REMEDICATION
FOR PATIENTS VALID FOR FDA DURATION OF ANALGESIA



Treatment	Calculated Time-to-Remedication		Tests[3]	
	Median Time (h:min)[1]	95% CI (h:min)[2]	Wilcoxon	Log Rank
Ketoprofen 12.5 mg	3:26	2:21 - 5:05	A	A
Acetaminophen 650 mg	3:19	3:00 - 5:01	A	A
Placebo	1:36	1:23 - 1:46	B	B

[1]Kaplan-Meier estimate
[2]Method of Simon and Lee, Cancer Treat Rep 66:37 - 42, 1982
[3]Wilcoxon and Log Rank test applied as in Fisher's PLSD

ESTIMATED DURATION OF ANALGESIA (TIME-TO-REMEDICATION)
PRODUCT LIMIT PLOT OF TIME TO REMEDICATION
FOR PATIENTS VALID FOR FDA DURATION OF ANALGESIA

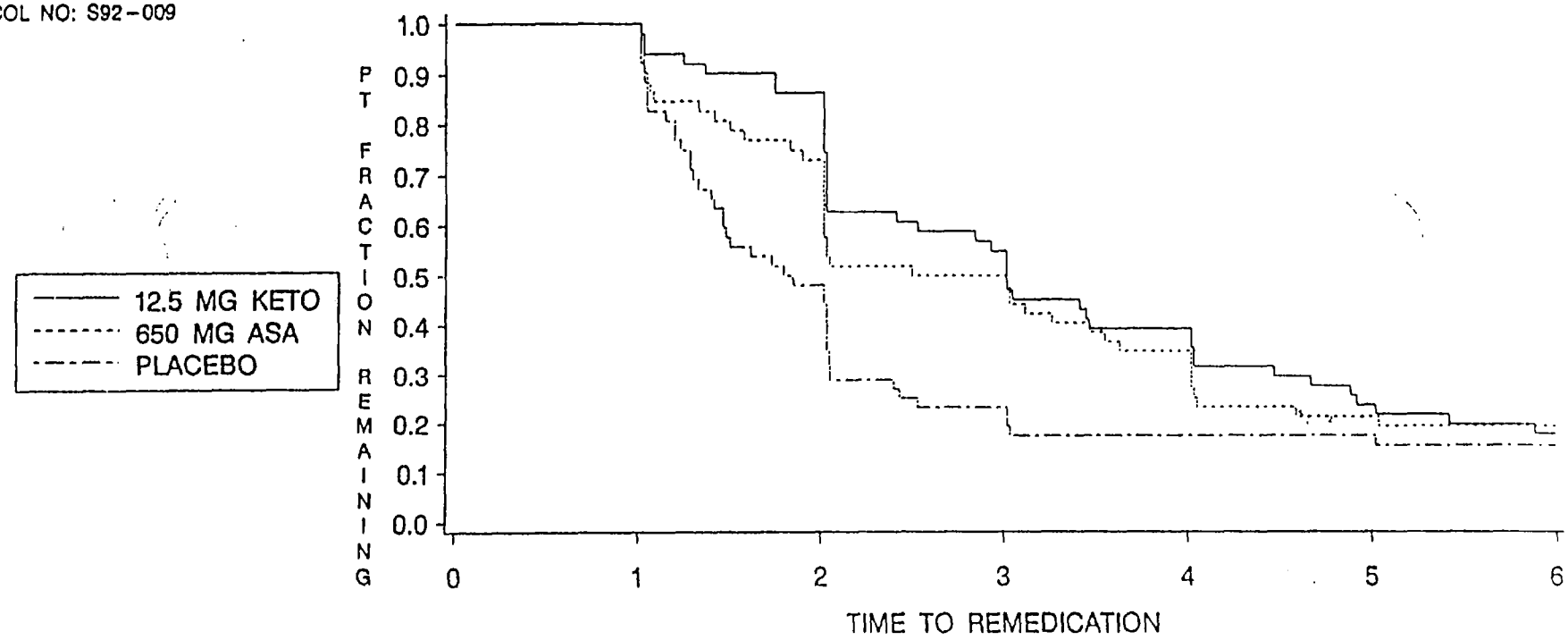


Treatment	Calculated Time-to-Remedication		Tests[3]	
	Median Time (h:min)[1]	95% CI (h:min)[2]	Wilcoxon	Log Rank
Ketoprofen 12.5 mg	> 6:00	> 6:00 - > 6:00	A	A
Ibuprofen 200 mg	> 6:00	> 6:00 - > 6:00	A	A
Placebo	1:20	1:06 - 1:32	B	B

[1]Kaplan-Meier estimate
[2]Method of Simon and Lee, Cancer Treat Rep 66:37 - 42, 1982
[3]Wilcoxon and Log Rank test applied as in Fisher's PLSD

ESTIMATED DURATION OF ANALGESIA (TIME-TO-REMEDICATION)
PRODUCT LIMIT PLOT OF TIME TO REMEDICATION
FOR PATIENTS VALID FOR FDA DURATION OF ANALGESIA

KETOPROFEN (BAY A 7790)/DENTAL
PROTOCOL NO: S92-009



Treatment	Calculated Time-to-Remedication		Tests[3]	
	Median Time (h:min)[1]	95% CI (h:min)[2]	Wilcoxon	Log Rank
Ketoprofen 12.5 mg	3:01	2:02 - 4:01	A	A
Aspirin 650 mg	2:46	2:01 - 3:38	A	AB
Placebo	1:50	1:25 - 2:02	B	B

[1]Kaplan-Meier estimate
[2]Method of Simon and Lee, Cancer Treat Rep 66:37-42, 1982
[3]Wilcoxon and Log rank test applied as in Fisher's PLSD

TABLE 1

TABLE 3.1
EFFICACY RESULTS
SUMMARY STATISTICS OBTAINED FROM ANALYSIS OF COVARIANCE
POPULATION:PATIENTS VALID FOR ANALYSIS OF EFFICACY
FDA REQUESTED VARIABLES

DRUG GROUP	TEMP DIF AUC 0 TO 6 HRS	TEMP DIF AUC 0 TO 8 HRS	MAX TEMP DIF 0 TO 6 HRS	MAX TEMP DIF 0 TO 8 HRS
KETO 25 MG				
N	30	30	30	30
MEAN	247.64	342.84	1.44	1.50
LSMEAN	244.36 A (1a)	337.81 A	1.43 A	1.49 A
STANDARD ERROR	32.03	38.53	0.14	0.13
RANGE				
KETO 12.5 MG				
N	30	30	30	30
MEAN	412.93	549.03	2.11	2.13
LSMEAN	418.77 B	557.99 BC	2.13 B	2.15 B
STANDARD ERROR	32.05	38.55	0.14	0.13
RANGE				
ACETA 650 MG				
N	30	30	30	30
MEAN	251.98	344.33	1.44	1.47
LSMEAN	244.15 A	332.32 A	1.42 A	1.44 A
STANDARD ERROR	32.07	38.58	0.14	0.13
RANGE				
PLACEBO				
N	30	30	30	30
MEAN	505.87	650.34	2.57	2.57
LSMEAN	511.14 C	658.42 C	2.58 C	2.58 C
STANDARD ERROR	32.04	38.55	0.14	0.13
RANGE				
P-VALUES				
TRT P (b)	0.0001	0.0001	0.0001	0.0001
TRT*BASELINE (c)	0.9200	0.9516	0.9939	0.9857

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05).
STATISTICS ARE BASED ON THE FISHER'S LSD COMPARISON (VERTICALLY).
(a) PLSD BASED ON MODEL (b) LSMEANS.
(b) MODEL: VAR= u + T(i) + B + error.
(c) MODEL: VAR= u + T(i) + B + B*T(i) + error.

NOTES: DIFFERENCE IS CALCULATED AS TEMPERATURE MINUS TEMPERATURE AT TIME OF ENDOTOXIN ADMINISTRATION.

TABLE 2

TABLE 11.1
EFFICACY RESULTS
SUMMARY STATISTICS OBTAINED FROM ANALYSIS OF VARIANCE
POPULATION: PATIENTS VALID FOR EFFICACY ANALYSIS (ACCORDING TO THE FDA CRITERIA)
FDA REQUESTED VARIABLES

DRUG GROUP	TEMP DIF AUC 0 TO 6 HRS	TEMP DIF AUC 0 TO 8 HRS	MAX TEMP DIF 0 TO 6 HRS	MAX TEMP DIF 0 TO 8 HRS
KETO 25 MG				
N	28	28	28	28
MEAN	419.52	466.02	2.07	2.08
LSMEAN	466.18 A(1a)	537.57 A	2.31 A	2.35 A
STANDARD ERROR	58.12	85.78	0.18	0.19
RANGE				
KETO 12.5 MG				
N	29	29	29	29
MEAN	325.55	348.72	1.93	1.93
LSMEAN	389.10 A	444.02 A	2.16 A	2.19 A
STANDARD ERROR	59.21	87.40	0.19	0.20
RANGE				
ACETA 650 MG				
N	26	26	26	26
MEAN	405.40	504.06	2.14	2.21
LSMEAN	437.05 A	567.27 A	2.27 A	2.38 A
STANDARD ERROR	60.75	89.68	0.19	0.20
RANGE				
PLACEBO				
N	29	29	29	29
MEAN	-73.29	-117.88	0.68	0.75
LSMEAN	-31.41 B	-52.25 B	0.85 B	0.96 B
STANDARD ERROR	55.35	81.70	0.17	0.18
RANGE				
P-VALUES				
TRT (b)	0.0001	0.0001	0.0001	0.0001
TRT*CENTER (c)	0.4833	0.3891	0.0384	0.0360
TRT*STRATUM (d)	0.8187	0.7550	0.8203	0.9245

(1) SAME LETTER INDICATES ABSENCE OF SIGNIFICANT DIFFERENCE (0.05 LEVEL).
STATISTICS ARE BASED ON THE FISHER'S LSD COMPARISON (VERTICALLY).
(a) PLSD BASED ON MODEL (b) LSMEANS.
(b) MODEL: VAR = u + T(i) + B(j) + C(r) + ERROR
(c) MODEL: VAR = u + T(i) + B(j) + C(r) + TC(ir) + ERROR
(d) MODEL: VAR = u + T(i) + B(j) + C(r) + TB(ij) + ERROR

NOTE: DIFFERENCE IS CALCULATED AS TEMPERATURE AT BASELINE MINUS
TEMPERATURE MEASURED AT EACH TIMEPOINT

TABLE 2A
SUMMARY OF PROTOCOL DEVIATIONS
POPULATION: VALID

TABLE 1

	NUMBER OF PATIENTS (%)		
	KETOPROFEN	IBUPROFEN	P-VALUE
TOOK MORE THAN ONE TABLET ON DAY 1/DOSE 1 *	507/3110 (16.30)	537/3094 (17.36)	0.267
TOOK MORE THAN 6 TABLETS IN 24 HOURS **	222/3109 (7.14)	232/3093 (7.50)	0.586
TOOK MORE THAN 6 TABLETS IN ONE CALENDAR DAY	74/3111 (2.38)	75/3094 (2.42)	0.907
LESS THAN 4 HOURS BEWTEEN DOSES (EXCEPT AFTER DOSE 1) *	384/3110 (12.35)	397/3094 (12.83)	0.566
TOOK MEDICATION MORE THAN 10 DAYS OR THREE DAYS WITH FEVER	87/3111 (2.80)	115/3094 (3.72)	0.041
MORE THAN 24 HOURS BETWEEN DOSES *** ¢	461/2783 (16.56)	473/2766 (17.10)	0.594
TOOK RESCUE MEDICATION PRIOR TO SECOND DOSE	23/3111 (0.74)	21/3094 (0.68)	0.776
TOOK RESCUE MEDICATION AND CONTINUED STUDY MEDICATION	25/3111 (0.80)	39/3094 (1.26)	0.075
EXPERIENCED NO RELIEF, BUT DID NOT TAKE RESCUE MEDICATION ¢¢	58/3109 (1.87)	68/3094 (2.20)	0.354
TOOK MORE THAN 2 TABLETS/DOSE	51/3111 (1.64)	38/3094 (1.23)	0.173
USED FOR "OTHER" INDICATION NOT IN LABEL	145/3111 (4.66)	166/3094 (5.37)	0.204
AT LEAST ONE INCIDENCE OF NONCOMPLIANCE	1322/3111 (42.49)	1348/3094 (43.57)	0.393
AT LEAST ONE INCIDENCE OF OVER DOSING	972/3111 (31.24)	1033/3094 (33.39)	0.071
ALL PATIENTS	3111	3094	

* PATIENT 6807 WAS REMOVED FROM RISK OF THIS PROTOCOL DEVIATION BECAUSE THIS PATIENT WAS MISSING AT LEAST ONE DOSING TIME WHICH PLACED THE PATIENT'S STATUS IN QUESTION

** PATIENTS 6807,15314, AND 15318 WERE REMOVED FROM RISK OF THIS PROTOCOL DEVIATION BECAUSE THEY WERE MISSING AT LEAST ONE DOSING TIME WHICH PLACED THEIR STATUS IN QUESTION

*** PATIENT 15318 WAS REMOVED FROM RISK OF THIS PROTOCOL DEVIATION BECAUSE PATIENT WAS MISSING AT LEAST ONE DOSING TIME WHICH PLACED PATIENTS STATUS IN QUESTION

¢ PATIENTS WITH MENSTRUAL CRAMPS ARE NOT AT RISK

¢¢ PATIENTS WITH NO RELIEF ARE NOT AT RISK

TABLE 2A
INCIDENCE OF ADVERSE EVENTS IN NON-COMPLIANT PATIENTS

TABLE 2

	NO OF PATIENTS WITH AT LEAST ONE TREATMENT EMERGENT ADVERSE EVENT /NO OF PATIENTS NONCOMPLIANT (%)		
	KETOPROFEN	IBUPROFEN	P-VALUE
TOOK MORE THAN ONE TABLET ON DAY 1/DOSE 1	29/ 507 (5.72)	16/ 507 (2.98)	0.029
TOOK MORE THAN 6 TABLETS IN 24 HOURS	23/ 222 (10.36)	21/ 232 (9.05)	0.638
TOOK MORE THAN 6 TABLETS IN ONE CALENDAR DAY	7/ 74 (9.46)	9/ 75 (12.00)	0.616
LESS THAN 4 HOURS BETWEEN DOSES (EXCEPT AFTER DOSE 1)	45/ 384 (11.72)	45/ 397 (11.34)	0.867
TOOK MEDICATION MORE THAN 10 DAYS OR THREE DAYS WITH FEVER	9/ 87 (10.34)	14/ 115 (12.17)	0.685
MORE THAN 24 HOURS BETWEEN DOSES	38/ 461 (8.24)	32/ 473 (6.77)	0.391
TOOK RESCUE MEDICATION PRIOR TO SECOND DOSE	5/ 23 (21.74)	3/ 21 (14.29)	0.701
TOOK RESCUE MEDICATION AND CONTINUED STUDY MEDICATION	2/ 25 (8.00)	4/ 39 (10.26)	1.000
EXPERIENCED NO RELIEF, BUT DID NOT TAKE RESCUE MEDICATION	9/ 58 (15.52)	4/ 68 (5.88)	0.076
TOOK MORE THAN 2 TABLETS/DOSE	2/ 51 (3.92)	1/ 38 (2.63)	1.000
USED FOR "OTHER" INDICATION NOT IN LABEL	11/ 145 (7.59)	20/ 166 (12.05)	0.190
AT LEAST ONE INCIDENCE OF NONCOMPLIANCE	122/1322 (9.23)	90/1348 (6.68)	0.015
AT LEAST ONE INCIDENCE OF OVER DOSING	82/ 972 (8.44)	67/1033 (6.49)	0.096

APPENDIX C

TABLE 1. ADVERSE EVENT SUMMARY - PART I

(Note: Sev stands for severe AEs. Rel stands for probably or possibly study drug-related AEs.)

	Ketoprofen			***Ibuprofen***			***Placebo***			***Acetaminophen***			***Aspirin***		
Subjects exposed	***N=4030***			***N=3446***			***N=515***			***N=108***			***N=52***		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	***470 (11.7)***	***42***	***290***	***247 (7.2)***	***22***	***171***	***101 (19.6)***	***15***	***32***	***53 (49.1)***	***6***	***18***	***11 (21.1)***	***0***	***8***
Body as a whole	174 (4.3)	19	58	52 (1.5)	11	25	71 (13.8)	12	14	38 (35.2)	2	3	3 (2.8)		3
Abdominal pain	36 (0.9)	8	32	16 (0.5)	4	15				3 (2.8)					
Back pain	4 (0.1)	1													
Accidental injury	3 (0.1)	1		1 (0)											
Allergic reaction				1 (0)	1	1									
Asthenia	8 (0.2)		5	6 (0.2)	1	2	4 (0.8)			5 (4.6)	1				
Chills	50 (1.2)	1		1 (0)		1	24 (4.7)	1		20 (18.5)					
Fever	60 (1.5)		2	1 (0)			31 (6.0)			24 (22.2)					
Flu syndrome	3 (0.1)			1 (0)			1 (0.2)								

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*
# of subj with any adverse events	*470 (11.7)*	*42*	*290*	*247 (7.2)*	*22*	*171*	*101 (19.6)*	*15*	*32*	*53 (49.1)*	*6*	*18*	*11 (21.1)*	*0*	*8*
Edema	1 (0)		1												
Malaise	1 (0)														
Moniliasis	1 (0)														
Pain	1 (0)		1	2 (0.1)		1	1 (0.2)								
Face edema	3 (0.1)		2	2 (0.1)		1									
Headache	74 (1.8)	10	16	23 (0.7)	5	4	53 (10.3)	11	14	17 (15.7)		3	3 (5.8)		3
Neck pain	1 (0)														
Neck rigidity							1 (0.2)								
Chest pain							1 (0.2)			1 (0.9)	1				
Cardiovascular syst	15 (0.4)	2	10	3 (0.1)		3	5 (1.0)			1 (0.9)			3 (5.8)		2
Palpitation	1 (0)	1	1				1 (0.2)								
Tachycardia	2 (0)		1	1 (0)		1									
Cardiovascular disorder										1 (0.9)					

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*
# of subj with any adverse events	*470 (11.7)*	*42*	*290*	*247 (7.2)*	*22*	*171*	*101 (19.6)*	*15*	*32*	*53 (49.1)*	*6*	*18*	*11 (21.1)*	*0*	*8*
Hemorrhage													1(1.9)		
Hypertension	1 (0)														
Hypotension							2 (0.4)								
Peripheral edema	3 (0.1)		1												
Vasodilatation	9 (0.2)	1	7	3 (0.1)		3	2 (0.4)						2 (3.8)		2
Digestive system	178 (4.0)	15	150	106 (3)	6	91	27 (5)	1	14	6 (6)		6	2 (4)		
Dry Mouth	11 (0.3)	2	10	6 (0.2)		4	1 (0.2)								
Gum hemorrhage							1 (0.2)						1 (1.9)		
Tooth pain	2 (0)			1 (0)											
Colitis	1 (0)		1												
Constipation	3 (0.1)		2	3 (0.1)	1	1									
Diarrhea	18 (0.4)	5	14	7 (0.2)		6	3 (0.6)		2	1 (0.9)					
Esophagitis	1 (0)		1												

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	***470 (11.7)***	***42***	***290***	***247 (7.2)***	***22***	***171***	***101 (19.6)***	***15***	***32***	***53 (49.1)***	***6***	***18***	***11 (21.1)***	***0***	***8***
Dyspepsia	72 (1.8)	1	64	56 (1.6)	2	52	1 (0.2)		1	1 (0.9)					
Eructation	1 (0)		1												
Flatulence	9 (0.2)		7	6 (0.2)	1	5									
Gastrointestinal disorder	2 (0)		1	1 (0)		1									
Melena	1 (0)	1	1												
Nausea	65 (1.6)	4	54	26 (0.8)	2	22	22 (4.3)	1	11	6 (5.6)		6	1 (1.9)		
Thirst	3 (0.1)	1	1	1 (0)		1									
Vomiting	6 (0.1)	3	3	3 (0.1)		2	6 (1.2)		1				1 (1.9)		
Increased salivation	1 (0)		1												
Gastritis				1 (0)		1									
Hemic & lymphatic				1 (0)						1 (0.9)					
Ecchymosis				1 (0)											
Lymphangitis										1 (0.9)					

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*
# of subj with any adverse events	*470 (11.7)*	*42*	*290*	*247 (7.2)*	*22*	*171*	*101 (19.6)*	*15*	*32*	*53 (49.1)*	*6*	*18*	*11 (21.1)*	*0*	*8*
Metabolic and nutritional	3 (0.1)		1												
Hypoglycemia	1 (0)		1												
Hyperlipemia	1 (0)														
Weight gain	1 (0)														
Musculoskeletal system	34 (0.8)	4	1	2 (0.1)	1	2	17 (3.3)			10 (9.3)					
Joint disorder	1 (0)														
Leg cramps	1 (0)														
Myalgia	30 (0.7)	4	1				17 (3.3)			10 (9.3)					
Myasthenia	1 (0)			2 (0.1)	1	2									
Surgery	1 (0)														
Nervous system	128 (3.2)	3	91	78 (2.3)	3	58	28 (5.4)	3	9	15 (13.9)		8	5 (9.6)		5
Abnormal dreams				1 (0)											

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	*470 (11.7)*	*42*	*290*	*247 (7.2)*	*22*	*171*	*101 (19.6)*	*15*	*32*	*53 (49.1)*	*6*	*18*	*11 (21.1)*	*0*	*8*
Anxiety	1 (0)			1 (0)		1									
Confusion				4 (0.1)		2							1 (1.9)		1
Convulsion				1 (0)	1										
Depersonalization				1 (0)											
Depression	2 (0)	1	2												
Dizziness	57 (1.4)	1	41	25 (0.7)	1	19	18 (3.5)	3	3	4 (3.7)		1			
Euphoria	1 (0)		1												
Hyperkinesia				2 (0.1)		1									
Hypertonia	1 (0)														
Insomnia				5 (0.1)		2									
Nervousness	6 (0.1)		4	3 (0.1)		2							1 (1.9)		1
Sleep disorder				1 (0)											
Somnolence	61 (1.5)	1	44	37 (1.1)	1	32	10 (1.9)		6	12 (11.1)		7	3 (5.8)		3

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	***470 (11.7)***	***42***	***290***	***247 (7.2)***	***22***	***171***	***101 (19.6)***	***15***	***32***	***53 (49.1)***	***6***	***18***	***11 (21.1)***	***0***	***8***
Vertigo	2 (0)		2												
Hypesthesia	1 (0)									1 (0.9)					
Paresthesia	3 (0.1)		3	2 (0.1)		2									
Respiratory system	37 (0.9)	2	1	20 (0.6)		2	9 (1.7)	1		4 (3.7)	3		1 (1.9)		
Asthma				1 (0)											
Cough increased	6 (0.1)						1 (0.2)								
Hyperventilation				1 (0)		1									
Yawn				1 (0)		1									
Bronchitis	4 (0.1)						1 (0.2)								
Pneumonia	2 (0)									1 (0.9)	1				
Pharyngitis	7 (0.2)			3 (0.1)			3 (0.6)			2 (1.9)	1				
Epistaxis	1 (0)			1 (0)			1 (0.2)						1 (1.9)		
Rhinitis	17 (0.4)	1		10 (0.3)			3 (0.6)			1 (0.9)					

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	***470 (11.7)***	***42***	***290***	***247 (7.2)***	***22***	***171***	***101 (19.6)***	***15***	***32***	***53 (49.1)***	***6***	***18***	***11 (21.1)***	***0***	***8***
Sinusitis	8 (0.2)	1	1	3 (0.1)			3 (0.6)	1		1 (0.9)	1				
Skin & appendages	13 (0.3)	1	7	7 (0.2)	2	3	1 (0.2)			3	1	2			
Acne	1 (0)	1	1												
Rash	5 (0.1)		3	3 (0.1)	1	3									
Urticaria	3 (0.1)		2	1 (0)						1 (0.9)		1			
Dry skin				1 (0)						1 (0.9)	1	1			
Pruritus	4 (0.1)		3	1 (0)											
Sweating	3 (0.1)			1 (0)	1		1 (0.2)			1 (0.9)					
Special senses	25 (0.6)	2	10	7 (0.2)		4	1 (0.2)			3 (2.8)					
Ear disorder	3 (0.1)			1 (0)											
Ear pain	2 (0)	1		2 (0.1)						1 (0.9)					
Otitis media										1 (0.9)					
Tinnitus	4 (0.1)		2												

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	***470 (11.7)***	***42***	***290***	***247 (7.2)***	***22***	***171***	***101 (19.6)***	***15***	***32***	***53 (49.1)***	***6***	***18***	***11 (21.1)***	***0***	***8***
Abnormal vision	3 (0.1)		1	1 (0)		1									
Amblyopia	4 (0.1)	1	3				1 (0.2)								
Conjunctivitis	2 (0)														
Dry eyes	1 (0)														
Eye disorder	1 (0)														
Photophobia	2 (0)									1 (0.9)					
Taste perversion	4 (0.1)		4	3 (0.1)		3									
Uro-genital system	10 (0.2)	1	2	6 (0.2)		1	4 (0.8)		1						
Female lactation	2 (0)			1 (0)			1 (0.2)								
Menorrhagia	1 (0)		1	1 (0)		1									
Menstrual disorder	1 (0)						1 (0.2)		1						
Metrorrhagia				1 (0)											
Vaginitis	2 (0)						1 (0.2)								

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*		
Subjects exposed	*N=4030*			*N=3446*			*N=515*			*N=108*			*N=52*		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	*470 (11.7)*	*42*	*290*	*247 (7.2)*	*22*	*171*	*101 (19.6)*	*15*	*32*	*53 (49.1)*	*6*	*18*	*11 (21.1)*	*0*	*8*
Cystitis	1 (0)	1													
Dysuria				1 (0)											
Polyuria	1 (0)														
Urinary frequency	1 (0)														
Urinary tract infection	1 (0)			2 (0.1)			1 (0.2)								
Urine abnormality	1 (0)		1												

APPENDIX C

TABLE 2. ADVERSE EVENT SUMMARY - PART II

(Note: Sev stands for severe adverse events; Rel stands for probably or possibly study drug-related adverse events)

	Ketoprofen			***Ibuprofen***			***Placebo***			***Acetaminophen***			***Aspirin***			***NAP***		
Subjects exposed	***N=1248***			***N=354***			***N=192***			***N=82***			***N=71***			***N=85***		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	***65 (5.2)***	***4***	***28***	***14 (4.0)***	***4***	***12***	***12 (6.3)***	***0***	***2***	***0***			***0***			***1(1.2)***	***0***	***1***
Body as a whole	26 (2.1)	1	9	2 (0.6)		2	3 (1.6)									1 (1.2)		1
Abdominal pain	9 (0.7)		5	1 (0.3)		1										1 (1.2)		1
Back pain	1 (0.1)	1																
Accidental injury	5 (0.4)																	
Allergic reaction	1 (0.1)		1															
Chills	1 (0.1)		1															
Malaise	1 (0.1)																	
Headache	11 (0.9)		2	1 (0.3)		1	3 (1.6)											