CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-938

MEDICAL REVIEW

DIV FILE # 20938

NDA 20-938

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Alan V. McEmber
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

DEC 15 1999

Dear Mr. McEmber:

Please refer to your new drug application (NDA) dated December 15, 1998, received December 16, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mobic® (meloxicam) 7.5 mg Tablets.

We acknowledge receipt of your submissions dated December 28, 1998, February 4, 17, 18, 19, 26, March 3, 29, 30, April 1, 2, 6, 15(2), 16, 22, June 10, 16, July 1, 7, 8, 12, 23, 28 (2), 30, August 3, 5, 6 (2), 9 (3), 11, 12, (2), 17, 19, 20, 27, 30, 31, September 1, 3, 9, 10, 13, 14, 21, October 19, November 19, 23, 30, December 1, 2, 6, 7 and 15, 1999.

This new drug application provides for the use of Mobic® (meloxicam) 7.5 mg Tablets for relief of signs and symptoms of osteoarthritis.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling for the drug product revised as recommended in the enclosed revised draft labeling text for the package insert. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the label may be required.

We note that the product labeling issues that have not yet been resolved to our mutual satisfaction primarily concern the description of the mechanism of action, and how certain features of the Mobic adverse event profile should be communicated in labeling. Please contact us if we can provide further assistance, and submit for review any additional information regarding these issues.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Any information suggesting a substantial difference from the previously reported rates of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Anthony M. Zeccola, Senior Regulatory Management Officer, at (301) 827-2090.

Sincerely,

/S/ 15 December 1999

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

MEDICAL OFFICER REVIEW of NDA LABELING and SAFETY UPDATE

NDA: 20-938
Drug: MELOXICAM
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
Letter Date: February 11, 2000
Review Date: March 13, 2000
Attachments: Approvable letter (Dec. 15, 1999), Final Draft Labeling

Background: Meloxicam was sent an approvable letter (attached) on December 15, 1999, pending agreement on acceptable labeling (attached). The labeling discussions prior to issuing the letter revolved around fair and balanced display of the evidence, especially that pertaining to serious GI adverse events.

Review and Discussion:

Cox 2 Selectivity: The agency and the sponsor engaged in a series of labeling discussions centering on the nature of the meloxicam submission vis-a-vis the Cox 2 hypothesis that there may be a lower incidence of serious GI adverse events due to selective inhibition of COX2 rather than COX1 enzyme. It was the agency's position that there was insufficient pharmacology and endoscopy information to support a COX2 mechanism of action for Meloxicam. The sponsor also conducted a post hoc, combined analysis of serious GI adverse events, but agency felt that the uncertainty in post hoc inferences could not justify their inclusion as labeling. However, there was a clear signal of a higher rate of serious GI adverse events at the 30mg/day dose (seen early in development, see Medical Officer Safety Review, pp23-4), which was included in the label (after Table 3, Final Draft Labeling).

Adverse Event Tables: The clinical trial database was dominated by two large trials, but of only one month duration. These were equivalence designs, and used only an active control. There was no placebo anchor to assure assay sensitivity, making their inferences less reliable. Accordingly, they are represented in the label (Table 3) simply as adverse event rate lists for the two meloxicam doses (7.5mg/day and 15mg/day), divided by duration (4-6 weeks trials versus 6 months trials), without any comparator rates. The 12-week, US trial was the strongest design, having both a placebo and active-control, and for this reason it is represented with meloxicam and control agents adverse event rate lists (Table 2).

Safety Update: A safety update, covering patient information up to a cutoff date of November 19,1999, and including a total of an additional 2249 patients exposed to meloxicam in clinical trials, was also submitted on February 11, 2000. These data added no new dimension to the labeling discussions generally. Only three new terms, confusion, bullous eruption, and increased creatinine, were added to the Adverse Reactions section.

Recommendation/Conclusion: The attached Final Draft Labeling is acceptable.

/S/ 3/27/00

Kent Johnson, MD, Medical Reviewer

/S/ 3/27/00

Karen Midthun, MD, Team Leader

REVIEW

Medical Officer's Review of NDA 20-938

NDA #20-938 — Submission 12/15/98
M.O. Review — Review completed 8/31/99

Proposed trade name:	Mobic
Generic name:	Meloxicam
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
Proposed Indication:	Symptoms of Osteoarthritis
Route of Administration:	Oral

/S/

Medical Reviewer: Kent Johnson, M.D. 12/9/99

/S/ 12-9-99

Deputy Director: John Hyde, M.D., Ph.D.

MELOXICAM EFFICACY REVIEW

INDEX:

INTRODUCTION

Meloxicam is a nonsteroidal anti-inflammatory drug of the oxicam class under development for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and other rheumatic and pain conditions. This NDA is for osteoarthritis alone. The drug chemically is 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, with an empirical formula of C14H13N3O4S2.

SUMMARY OF PHARMACOKINETICS: Meloxicam pharmcokinetics were characterized by an 89% bioavailability, with maximum plasma concentrations attained in 5-6 hours postdose, and steady state withing 3-5 days. Multiple dosing studies showed dose proportionality in the 7.5 to 30mg range. Binding to serum protein is very high (>99%), so the volume of distribution is small (0.14L/kg). The drug is metabolized to four inactive products, excreted roughly equally in the urine and in the feces. Total clearance was between 7 and 9 mL/min, with an apparent elimination half-life of between 15 and 20 hours. See Pharmacokinetics Review for further details.

CLINICAL PHARMACOLOGY

Meloxicam showed ex vivo inhibition of platelet aggregation in the human blood assay at 7.5mg and 15mg doses, and preferential inhibition of COX-2 (by lipopolysaccharide stimulated of PGE2 synthesis in whole blood) over COX-1 (by thromboxane A2 synthesis by clotting whole blood). See Pharmacology Review for other studies. They did not report endoscopy data.

TRIAL DATABASE LISTING

INTRODUCTION: The sine qua non of an assertion of successful efficacy demonstration in an OA trial result is valid and accurate evidence representative of the totality of OA. There is now international agreement on the domains which should be represented in this totality -- pain, function, and the patient global (PG). If a longterm demonstration is intended, structure measurement is also recommended. Confounders such as rescue medication use need to be addressed. This review uses these four parameters -- pain, function, patient global, and use of rescue medication -- as primary in its assessment of the efficacy results of randomized trials.

The meloxicam OA submission consists of 17 randomized, double-blind clinical trials (RCTs). Eight (8) trials -- two placebo-control (#181, 042) and six active-control (#043,044,045,063,153,154) -- used designs which were adequate and conventional enough to describe and analyze using modern OA assessment methodology. Active-control doses were either piroxicam 20mg or diclofenacSR 100mg. These trials constitute the primary evidence for demonstration of efficacy in OA. The one month results are shown in the Summary Efficacy Table below, and individual trial summaries are included at the end of this review. The remaining nine trials use designs which test non-conventional hypotheses, and often use non-conventional (and sometimes culturally specific) endpoints. These trials are summarized at the end of this narrative.

Only trial #181 was done in the U.S., and it was the only trial using both a placebo and an active control. It also was the only trial requiring a formal flare of symptoms for entry. Other trials required medication washout, and all trials required for entry pain-on-motion of greater than 35mm on a 100mm visual analog scale scale, described as the "worst pain in last 24hr" (trials #042,043,044) or "overall pain during last week" (trials #045,063).

Typically, OA trials use multiple endpoints. Those use here correspond to the domains noted above: (1) a patient global (PG), measured on a 0-4 Likert or 0-10cm VAS scale, (2) a patient pain (similarly measured), and (3) a function measure (typically the WOMAC or Lequesne self administered questionaires, both validated for knee and hip OA (see OA Guidance Document Draft). Data on rescue medication use (typically, acetominophen, to 4gm/d) was collected in all trials except two (#153 and 154, where no rescue medication was allowed), and analyzed as the fourth primary efficacy variable. The list below shows the duration, time, place, and endpoints for these eight trials.

EIGHT OA TRIALS PROVIDING PRIMARY EVIDENCE FOR EFFICACY

Trial/date/dur	OA type	arms:mel	control	endpts:PG	pain	fctn	rescue
PLACEBO/CONTROL							
181-97 3mo	hip/knee(US)	3.75, 7.5, 15	plc,diclofenac	x	x	x	x
042-89 3wk	knee(Eur)	7.5, 15, 30*	plc	x	x	x	x
ACTIVE-CONTROL							
043-90 6wk	hip(Eur)	15,30*	piroxicam	x	x	x	x
044-90 6wk	knee(Eur)	15,30*	diclofenac	x	x	x	x
045-89 6mo	kn/hip(Eur)	15	piroxicam	--	x	x	x
063-90 6mo	kn/hip(Eur)	7.5	diclofenac	--	x	x	x
153-95 1mo	kn/hip/sp(Eur)	7.5	diclofenac	x	x	--	--
154-95 1mo	kn/hip/sp(Eur)	7.5	piroxicam	x	x	--	--

*=30mg dose discontinued, 6/1990, due to GI toxicity

OVERALL EFFICACY

The summary efficacy table below lists p values or qL values (the lower 95% confidence limit for the ratio of change from baseline to month one or nearest timepoint, for the test to the change for the active control) for comparisons of the four efficacy variables in the eight primary trials. A qU (the upper 95% confidence limit) result of less than 1.00 means the active control / meloxicam comparison shows a $p<0.05$. The one month timepoint is used to minimize dropouts, which are usually minimal at this point. Subsequent timepoints in trials #043, 044, 045, and 063 showed consistent results. All analyses were intent-to-treat / last-observation-brought-forward, adjusted for center effects, and (for trials #181, 045 and 063) the effect of signal joint location (knee or hip). Baseline value proved not significant enough to include as a covariate. The degree of flare in trial #181 did impact results, although not enough to change any statistical conclusion. Rescue medication did not prove a strong co-variate, but, as noted above, it is treated as an independent variable.

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ON ORIGINAL

SUMMARY EFFICACY TABLE

Trial	dur	OA (size)	arms (mel/controls)		PG	pain	fctn.	rescue
181	3mo	knee/hip (n=779)	1mo	3.75m	0.009	0.089	0.007	0.116
	25-49% d/o's		p values	7.5mg	<0.001	<0.001	0.001	0.041
	(ITE d/o: p<0.05, all arms)		vs plc.	15mg	<0.001	<0.001	<0.001	0.044
				dicl.				<0.001
			1mo	3.75m	0.56	0.51	0.54	0.723#
			qL values	7.5mg	0.68	0.70	0.60	0.735
			vs dicl.	15mg	0.75	0.77	0.73	0.716#
042	3wk	knee (n=513)		7.5mg	0.094	0.022	0.653	0.664
	6-13% d/o's		3wk p values	15mg	0.003	0.036	0.066	0.196
	(ITE:0-1%)		vs plc	30mg	0.002	0.004	0.044	0.485
043	6wk	hip (n=285)	6wk qL values		0.95	0.90	0.88	0.81
	12% d/o's (ITE:2-3%)		15mg mel. vs pir.					
044	6wk	knee (n=268)	6wk qL values		0.98	0.94	0.84	0.91
	21-23% d/os (ITE:2-4%)		15mg mel. vs dicl.					
045	6mo	knee/hip (n=455)	1mo qL values		----	0.79	0.63*	0.92
	27-34% d/o's (ITE:2-3%)		15mg mel. vs pir.					
063	6mo	knee/hip (n=336)	1mo qL values		----	0.82	0.64*	0.84
	27-34% d/o's (ITE:4%)		7.5mg mel. vs pir.					
153	1mo	KNEE (n=4349)	1mo qL values		0.95#	0.91	----	----
	10-11% d/o's (ITE:1-2%)		7.5mg mel vs dicl.					
	1mo	HIP (n=1590)	1mo qL values		0.93#	0.86	----	----
	7-10% d/o's (ITE:1-2%)		7.5mg mel. vs dicl.					
	1mo	SPINE/HDS(n=4112)	1mo qL values		0.94#	0.89#	----	----
	8-11% d/o's (ITE:1%)		7.5mg mel. vs dicl.					
154	1mo	KNEE (n=4216)	1mo qL values		0.96	0.90#	----	----
	9-10% d/o's (ITE:2%)		7.5mg mel. vs pir.					
	1mo	HIP (n=1312)	1mo qL values		0.96	0.83	----	----
	8-10% d/o's (ITE:1-2%)		7.5mg mel. vs pir.					
	1mo	SPINE/HDS(n=3758)	1mo qL values		0.97	0.91	----	----
	11-13% d/o's (ITE:2%)		7.5mg mel. vs pir.					

qU<1.00, implying p<0.05
* 2 mo data

EFFICACY ASSESSMENT

METHODOLOGY

PLACEBO-CONTROL EVIDENCE: The analysis used here is the traditional method used at the agency for OA efficacy assessment, requiring 3/4 of the primary efficacy variables to show statistical significance by $p<0.05$ without adjustment for multiplicity. Endpoints used in the past were the two globals (patient and investigator), a patient pain scale, and a fourth endpoint reflecting the investigator's physical examination of the signal joint. However, in accordance with the international consensus of essential domains for OA assessment, pain, patient global, and a self-administered function questionaire are now used as primary efficacy endpoints, with rescue medication use added as the fourth. In the past, a comparison of proportionate inefficacy dropouts has been a useful barometer of efficacy, but with the exception of #181, these trials showed insufficient inefficacy dropouts for analysis.

ACTIVE-CONTROL EVIDENCE: Evidence of efficacy from active control designs without a placebo "anchor" have also been part of traditional NSAID NDAs, as they are frequently touted as an ethically preferable design. In this NDA they supply the evidence from six trials. From past experience, approvable NSAIDs have, in their active-control evidence, shown, in general, a lower limit of the 95% confidence interval of the ratio of the change-on-drug to the change-on-active-control greater than 0.60 for OA (0.70 for RA). A 3/4 test has conventionally been applied to these qL statistics, without correction for multiplicity. It should be noted that there was no prespecified "equivalence to NSAID" hypotheses here.

EFFICACY CONCLUSIONS

By the 3/4 criterion, trial #181 demonstrates efficacy for the 7.5 and 15 mg doses (see Summary Efficacy Table), and the results are replicated at other timepoints (see specific #181 writeup). Trial #042 (an early European study) is, at most, supportive, because the only arm succeeding (by the 3/4 test) is the 30mg dose, which proved too GI toxic and contributed to the decision to discontinue this dose about 75% into the study. By the $qL>0.60$ criterion, all meloxicam arms in all trials succeeded (26 comparisons in 6 trials, subseting the large trials #153 and 154 into knee, hip and spine/hands - see Summary Efficacy Table). In two instances all four endpoints were collected, and these succeeded by the 3/4 test. Trials #044 and 045 showed 3/3 of the results with a $qL>0.60$, replicated at the later timepoints in these two 6 month trials. The subsets of #153 and 154 showed 2/2 endpoint results with a $qL>0.60$. The latter two trials did not allow rescue medication use, nor did they measure a function questionaire. Since these trials were powered to show small safety differences, their size allowed very tight conference intervals, but this also increased the chance of detecting small efficacy differences, which occurred in 5/12 comparisons with the respective active control (signified by #, meaning a qU less than 1.00).

OVERALL EFFICACY CONCLUSION: Trial #181 is strongly supportive of an effect compared to placebo for both the 7.5 and 15mg dose, a $p<0.001$ result being, in some sense, equivalent to

two $p<0.05$ results. Also, both doses successfully matched the active control, and inefficacy dropouts show a statistically significant difference compared to placebo. Trial #042 is weaker, showing only 2/4 p values ≤ 0.05 for 15mg and 1/4 for 7.5mg, but this is outweighed by the consistency and robustness of the qL results for both 7.5 and 15mg across all six active-control trials. None of these trials had large numbers of dropouts except #181, in which the dropout pattern was consistent with a drug effect.

ANCILLARY EVIDENCE

Nine studies are included in this category. Four contributed data (see below), including #129 - a one month, dose-control, Japanese knee study, #131 - a one-month, Japanese knee study, and #196 and 213 - one month Taiwanese knee studies. Five studies did not contribute data: #149 and #190 - both ongoing, #099 - a 3 month quality-of-life, European hip study under analysis, #094 - enrolled spinal OA, and #046 was prematurely terminated (had used only the 30mg dose, stopped for toxicity (see Safety Review).

Trial	dur	OA (size)	arms (mel/controls)	PG	pain	fctn.	rescue
129	1mo	knee (n=222)	5mg vs 10mg	0.0006			
			5mg vs 15mg	0.0269			
			10mg vs 15mg	0.4097			
			(Tukey's multi-comparison)				
131	1mo	knee (n=212)	1mo qL values 10mg mel. vs dicl.75mg	0.62	0.79	0.77	
196	1mo 11-21% d/o's (ITE:1-4%)	knee/(hip) (n=282)	1mo qL values 7.5mg mel. vs dicl.	0.85	0.92	0.67	
213	1mo	knee (n=60)	1mo qL values 7.5mg mel. vs dicl.	0.90	0.69	0.03	

These data are consistent with the primary evidence above.

LONG-TERM EFFICACY

Long-term use of meloxicam comes only from trials #045 and 063, each of six months duration, at which point the results paralleled those at one month. Trial #047 was a long-term study of meloxicam 15mg/d for up to 24 months in 282 patients begun, de novo, on meloxicam 15mg/d, 211 trial #045 completers (143 of the 223 meloxicam completers, 68 of the 98 piroxicam completers). Thus, no exposure beyond six months is controlled, so only change from baseline and "survival" (still on treatment) comparisons are possible. Consequently no inference regarding long-term efficacy can be made. What can be asserted is that IF a patient tolerates the treatment for an initial period, he then has a given chance of tolerating it out to two years. This is a ***conditional*** inference.

The table below shows the disposition of patients in these three trials. 143 of the patients are counted twice, once in trial #045 asd once in trial #047.

TABLE 8.7.4.2: 1 Patient Disposition (Trials 107.045, 107.063, and 107.047)

	Trial 107.045		Trial 107.063		Trial 107.047
	Meloxicam 15 mg	Piroxicam 20 mg	Meloxicam 7.5 mg	Diclofenac 100 mg SR	Meloxicam 15 mg
Treated, N	306	149	169	167	490
Discontinued					
Due to Adverse Events, N (%)	45 (14.7)	28 (18.8)	21 (12.4)	31 (18.6)	97 (19.8)
Due to Lack of Efficacy, N (%)	9 (2.9)	3 (2.0)	7 (4.1)	7 (4.2)	22 (4.5)
Other[1], N (%)	29 (9.5)	20 (13.4)	17 (10.1)	19 (11.4)	97 (19.8)
Total Discontinued, N (%)	83 (27.1)	51 (34.2)	45 (26.6)	57 (34.1)	216 (44.1)
Completed, N (%)	223 (72.9)	98 (65.8)	124 (73.4)	110 (65.9)	274 (55.9)[2]

[1] Majority consists of discontinuations due to protocol violations and/or poor compliance.

[2] Of the patients who completed the trial, 131 (26.7%) chose not to participate in the optional extension to two years.

The following two tables show results from trial #045 out to two years for patient pain, and for the Notingham Health Profile, which evaluates physical mobility, energy level, social isolation and influences on various aspects of life, and so is a mixture of a physical function and quality-of-life measure. Improvements compared to baseline were sustained to two years in pain, and the lowering of the Nottingham scale by 2.5 corresponds to a $p<0.001$.

TABLE 8.7.4.4.2: 2 Statistical Results for Overall Pain[1] at Baseline and Change from Baseline at 12-Month Visit (LOCF)[2] and 24-Month Visit (LOCF)[2] by Subpopulation: Intent-to-Treat Population

Patient Population	Statistic	Baseline[3]	Change from Baseline	
		Visit 1	12-Month Visit (LOCF)[2]	24-Month Visit (LOCF)[2]
Direct Entry[4]	N	281	269	269
	Mean	63.0	-29.3	-29.7
	Std Dev	17.0	26.1	26.5
	Median	64.0	-32.0	-33.0
	95% CI[5]	–	-32.4, -26.1	-33.0, -26.5
	p-value[6]	–	<0.001	<0.001
Total Study Population	N	489	465	465
	Mean	63.0	-30.7	-30.7
	Std Dev	16.0	26.0	26.0
	Median	63.0	-33.0	-34.0
	95% CI[5]	–	-33.1, -28.3	-33.1, -28.2
	p-value[6]	–	<0.001	<0.001
Group I[7]	N	424	404	404
	Mean	63.0	-30.0	-31.0
	Std Dev	16.0	26.0	26.0
	Median	63.0	-32.0	-34.0
	95% CI[5]	–	-25.2, -21.2	-25.9, -22.0
	p-value[6]	–	<0.001	<0.001
Group II[8]	N	65	60	60
	Mean	63.0	-34.0	-30.0
	Std Dev	14.0	25.0	27.0
	Median	63.0	-37.0	-33.0
	95% CI[5]	–	-12.5, -8.5	-10.6, 6.6
	p-value[6]	–	<0.001	<0.001
Group Comparison (II-I)	Mean	–	-4.5	0.1
	95% CI	–	-10.7, 1.7	-6.1, 6.3
	p-value	–	0.152	0.972

[1] Overall pain was measured using a 100 mm VAS (0=no pain, 100=unbearable pain).
[2] LOCF = last observation carried forward.
[3] Baseline was determined after a washout period of at least three days in all patients previously treated with an NSAID.
[4] Direct entry = patients who were not previously enrolled in a meloxicam trial.
[5] 95% confidence interval for the mean change from baseline.
[6] P-value from the Student's t-test for the mean change from baseline.
[7] Group I = patients treated with meloxicam up to 24 months by either direct- or indirect-entry (indirect-entry included all meloxicam patients from Trial 107.045).
[8] Group II = indirect-entry patients who received meloxicam for up to 18 months (piroxicam patients from Trial 107.045).

TABLE 8.7.4.4.2: 3 Descriptive Statistics for Quality of Life Total Score at Baseline and Change from Baseline at 24-Month Visit (LOCF)[1] by Subpopulation: Intent-to-Treat Population

Patient Population	Statistic	Baseline	Change from Baseline
		Visit 1	24-Month Visit (LOCF)[2]
Direct Entry[3]	N	280	233
	Mean	6.9	-2.5
	Std Dev	4.5	3.7
	Median	7.0	-2.0
	Range		
Total Study Population	N	477	420
	Mean	6.2	-1.5
	Std Dev	4.6	3.6
	Median	5.0	-1.0
	Range		
Group I[4]	N	413	361
	Mean	6.3	-1.5
	Std Dev	4.7	3.6
	Median	6.0	-1.0
	Range		
Group II[5]	N	64	59
	Mean	5.4	0.0
	Std Dev	3.7	3.2
	Median	5.0	0.0
	Range		

MELOXICAM SAFETY REVIEW

ATTACHMENTS:

FDA memo re. definition of "clinically relevant (serious) UGI event" (12/8/98)

INDEX OF APPENDICES

PATIENT ACCOUNTABILITY / EXPOSURE

This safety database is naturally divided into exUS and US (trial #181) components. The OA exposure is 11,207 in the exUS and 464 in the US database, and these patients, along with those meloxicam patients treated in other indications, are shown in the table below. As of June, 1999, an additional 53,660 patients were exposed in post-marketing surveillance and observational surveys (34,791 in OA, 7,396 in RA, 14,088 in "other" indications).

Enumeration of Phase 2/3 Meloxicam-Treated Patients by Indication (Integrated Safety Database)

	OA[1]		RA[1]		AS		Other		TOTAL[1]	
	n	%	n	%	n	%	n	%	n	%
Phase 2/3										
Controlled	10787	69.8	1695	11.0	252	1.6	588	3.8	13322	86.2
Placebo Control	376	2.4	319	2.1	244	1.6	184	1.2	1123	7.3
Active Control	10411	67.4	1376	8.9	252	1.6	404	2.6	12443	80.5
Uncontrolled	421	2.7	1747	11.3	33	0.2	125	0.8	2324	15.0
≤6 months	296	1.9	535	3.5	33	0.2	125	0.8	989	6.4
>6 months	125	0.8	1306	8.4	-	-	-	-	1431	9.3
Total	11207	72.5	3253	21.0	285	1.8	713	4.6	15456	100

1 Two patients switched from OA in the source trial to RA in the follow-up trial and are counted once under each indication, but only once in the TOTAL column. These patients are: 107.077/714/96 (OA, 15mg), who became 107.069/1/470 (RA, 15mg); and 107.077/731/35 (OA, 15mg), who became 107.069/1/135 (RA, 15mg). Also, some patients participated in both controlled and uncontrolled trials, therefore the total patients exposed to meloxicam in controlled trials and those exposed in uncontrolled trials do not add to the total exposed.

The total ex-US database by dose is shown below.

Exposure by Meloxicam Dose - Phase 2/3 Trials (Integrated Safety Database)

Phase 2/3 Trials, Uncontrolled and Controlled		Treated Patients[1]		Duration of Therapy		Exposure (subject-years)
		n	%	n (patients)	mean (days)	
Meloxicam	7.5 mg	9968	64.5	9961	32.6	888.8
	15 mg	3349	21.7	3341	111.4	1019.3
	22.5 mg	884	5.7	883	240.1	580.6
	30 mg	1202	7.8	1200	46.2	151.9
	>30 mg	98	0.6	98	22.0	5.9
	TOTAL[2]	15456	100	15438	62.6	2646.4

1 The number of treated patients differs from the number of patients used for the calculation for duration of therapy because patients with missing treatment start or stop dates were excluded from the duration calculation.

The total exUS database by duration is shown below.

duration	7.5mg	15mg	22.5mg	30mg	>30mg
>0 days	9961	3341	883	1200	98
≥30 days	2628	1589	783	366	3
≥60 days	341	1254	709	238	1
≥180 days	157	514	592	70	
≥360 days	10	312	170		
≥540 days	4	96			

The total ex-US OA use in controlled trials.

Exposure - OA Active-Controlled and All Placebo-Controlled Phase 2/3 Trials (Integrated Safety Database)

Treatment Group	Treated Patients[1] n	Duration of Therapy[1] n (patients)	Duration of Therapy[1] mean (days)	Exposure (subject-years)
OA Active-Controlled Trials[2]				
Meloxicam (all doses)	10411	10402	33.7	960.8
Diclofenac SR	5243	5242	32.3	463.0
Piroxicam	4819	4814	31.0	408.3
All Placebo-Controlled Trials[2]				
Meloxicam (all doses)	1123	1120	67.6	207.4
Placebo	583	580	41.9	66.5

[1] The number of treated patients differs from the number of patients used for the calculation for duration of therapy because some patients were excluded from the duration calculation due to missing treatment start or stop dates.
[2] Trials using all formulations of meloxicam were included.

Exposure by Meloxicam Dose - OA Active-Controlled and All Placebo-Controlled Phase 2/3 Trials (Integrated Safety Database)

Meloxicam Dose	Meloxicam (All Doses) Treated Patients[1] n	%	Duration of Therapy n (patients)	Duration of Therapy mean (days)	Exposure (subject-years)
OA Active-Controlled Trials					
7.5 mg	9241	88.8	9234	29.9	756.8
15 mg	979	9.4	977	71.4	191.0
22.5 mg	-	-	-	-	-
30 mg	152	1.5	152	26.1	10.9
>30 mg	39	0.4	39	21.1	2.3
OA Active-Controlled TOTAL	10411	100	10402	33.7	960.8
All Placebo-Controlled Trials					
7.5 mg	297	26.4	297	20.9	17.0
15 mg	600	53.4	597	57.9	94.7
22.5 mg	124	11.0	124	264.9	89.9
30 mg	102	9.1	102	20.6	5.8
>30 mg	-	-	-	-	-
All Placebo-Controlled TOTAL[2]	1123	100	1120	67.6	207.4

Adding the single US OA trial (trial #181) -- 464: meloxicam, 153: diclofenac, and 158: placebo -- completes the exposure. The OA exposure in controlled settings is mainly from the two large, one month studies (#153 and #154) of 8955 patients and 682.5 patient-years exposure, 75% and 57% of the total patients and total patient-years, respectively.

DEMOGRAPHICS OF SAFETY DATABASE

The table below shows demographics for ex-US OA trials, and for US trial #181. These data are in no way atypical, and generally reflect the demographics of OA in Europe.

TABLE 8.8.5.1: 1 Demographics in Phase 2/3 Controlled Trials by Trial Type and Treatment Group (Integrated Safety Database)

Demographic Parameter	[redacted]		[redacted]		Other OA Active-Controlled Trials			Placebo-Controlled Trials	
	Meloxicam N=4635	Diclofenac N=4688	Meloxicam N=4320	Piroxicam N=4336	Meloxicam N=1164	Diclofenac N=555	Piroxicam N=335	Meloxicam N=1123	Placebo N=583
Age (years)									
Mean	61.5	61.7	61.3	61.6	63.7	64.5	64.2	53.6	49.5
Median	62.0	62.0	61.5	62.0	64.0	64.0	63.0	54.0	48.0
Range	[redacted]								
Groups									
Missing	6	12	8	12	0	0	0	0	0
≤40 years	263 5.7%	277 5.9%	228 5.3%	235 5.4%	29 2.5%	16 2.9%	2 0.6%	275 24.5%	189 32.4%
41-50 years	609 13.2%	596 12.7%	512 11.9%	503 11.6%	115 9.9%	46 8.3%	26 7.8%	197 17.5%	134 23.0%
51-60 years	1259 27.2%	1215 26.0%	1270 29.5%	1240 28.7%	309 26.5%	137 24.7%	115 34.3%	250 22.3%	92 15.8%
61-70 years	1291 27.9%	1387 29.7%	1269 29.4%	1270 29.4%	375 32.2%	181 32.6%	93 27.8%	221 19.7%	106 18.2%
71-80 years	937 20.2%	925 19.8%	809 18.8%	819 18.9%	246 21.1%	118 21.3%	76 22.7%	122 10.9%	46 7.9%
>80 years	270 5.8%	276 5.9%	224 5.2%	257 5.9%	90 7.7%	57 10.3%	23 6.9%	58 5.2%	16 2.7%
Gender									
Missing	3	6	6	10	0	0	0	0	0
Male	1536 33.2%	1538 32.8%	1390 32.2%	1427 33.0%	441 37.9%	177 31.9%	153 45.7%	510 45.4%	281 48.2%
Female	3096 66.8%	3144 67.2%	2924 67.8%	2899 67.0%	723 62.1%	378 68.1%	182 54.3%	613 54.6%	302 51.8%
Gender by Age									
Missing	7	12	10	12	0	0	0	0	0
Males ≤65 years	977 21.1%	970 20.7%	966 22.4%	967 22.4%	288 24.7%	116 20.9%	98 29.3%	438 39.0%	253 43.4%
Males >65 years	557 12.0%	566 12.1%	423 9.8%	460 10.6%	153 13.1%	61 11.0%	55 16.4%	72 6.4%	28 4.8%
Females ≤65 years	1808 39.1%	1776 38.0%	1734 40.2%	1690 39.1%	342 29.4%	179 32.3%	92 27.5%	392 34.9%	213 36.5%
Females >65 years	1286 27.8%	1364 29.2%	1187 27.5%	1207 27.9%	381 32.7%	199 35.9%	90 26.9%	221 19.7%	89 15.3%

Note: Patients with missing values were excluded from the denominator in the calculation of percentages.
Sources: TABLES D.6, D.5, and D.3

TABLE 8.8.5.1: 1 Demographics in Phase 2/3 Controlled Trials by Trial Type and Treatment Group (Integrated Safety Database) (Cont'd)

Demographic Parameter	[redacted]		[redacted]		Other OA Active-Controlled Trials			Placebo-Controlled Trials	
	Meloxicam N=4635	Diclofenac N=4688	Meloxicam N=4320	Piroxicam N=4336	Meloxicam N=1164	Diclofenac N=555	Piroxicam N=335	Meloxicam N=1123	Placebo N=583
Race									
Missing	1158	1212	4	10	337	146	147	465	184
Caucasian	3415 98.2%	3424 98.5%	4238 98.2%	4254 98.3%	800 96.7%	393 96.1%	181 96.3%	632 96.0%	387 97.0%
Black	51 1.5%	45 1.3%	61 1.4%	57 1.3%	6 0.7%	3 0.7%	1 0.5%	3 0.5%	-
Other	11 0.3%	7 0.2%	17 0.4%	15 0.3%	21 2.5%	13 3.2%	6 3.2%	23 3.5%	12 3.0%
Weight (kg)									
Mean	75.6	75.4	75.4	75.4	75.0	74.8	75.3	72.8	74.1
Median	75.0	74.0	74.0	74.0	75.0	74.0	74.0	72.0	74.0
Range	[redacted]								
Groups									
Missing	16	18	8	19	1	1	0	1	1
≤70 kg	1847 40.0%	1878 40.2%	1779 41.3%	1757 40.7%	446 38.5%	235 42.4%	133 39.7%	526 46.9%	229 39.3%
>70 kg	2772 60.0%	2792 59.8%	2533 58.7%	2560 59.3%	717 61.7%	319 57.6%	202 60.3%	596 53.1%	353 60.7%

Note: Patients with missing values were excluded from the denominator in the calculation of percentages.
Sources: TABLES D.6, D.5, and D.3

TABLE 8.3.1: 1 - Demographic Characteristics for All Treated Patients

		Treatment Group				
		Placebo (N=157)	Meloxicam 3.75 mg (N=154)	Meloxicam 7.5 mg (N=154)	Meloxicam 15 mg (N=156)	Diclofenac 50 mg BID (N=153)
Sex	Male	55 (35.0%)	51 (33.1%)	57 (37.0%)	56 (35.9%)	49 (32.0%)
	Female	102 (65.0%)	103 (66.9%)	97 (63.0%)	100 (64.1%)	104 (68.0%)
Race	Caucasian	143 (91.1%)	139 (90.3%)	141 (91.6%)	140 (89.7%)	136 (88.9%)
	Negroid	10 (6.4%)	9 (5.8%)	8 (5.2%)	7 (4.5%)	13 (8.5%)
	Mongoloid	4 (2.5%)	6 (3.9%)	5 (3.2%)	9 (5.8%)	4 (2.6%)
Age (yrs.)	< 40	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	40 – 50	24 (15.3%)	23 (14.9%)	20 (13.0%)	11 (7.1%)	17 (11.1%)
	51 – 60	44 (28.0%)	39 (25.3%)	48 (31.2%)	46 (29.5%)	48 (31.4%)
	61 – 70	50 (31.8%)	55 (35.7%)	49 (31.8%)	58 (37.2%)	45 (29.4%)
	71 – 80	34 (21.7%)	32 (20.8%)	35 (22.7%)	34 (21.8%)	41 (26.8%)
	> 80	5 (3.2%)	4 (2.6%)	2 (1.3%)	7 (4.5%)	1 (0.7%)
	Mean ± SD	62.3 ± 10.8	62.3 ± 10.5	62.4 ± 10.2	64.3 ± 9.9	63.0 ± 10.0
Weight (lbs.)	Mean ± SD	197.4 ± 55.2	201.1 ± 49.2	203.1 ± 48.5	194.2 ± 47.9	204.4 ± 47.0
Height (in.)	Mean ± SD	65.9 ± 4.2	65.9 ± 4.2	66.2 ± 4.2	66.0 ± 3.9	65.8 ± 4.2

Source: APPENDIX 15.9.2, TABLE 2.1

The mean age of patients in each of the five treatment groups ranged from 62 to 64 years. The age range of patients in the trial was between 37 and 93 years and was consistent across all treatment groups (APPENDIX 15.9.2, TABLE 2.1). In each of the treatment groups, between 32% and 37% of the patients were male. The vast majority of patients in each treatment group (between 89% and 92%) were Caucasian. Of the 28 patients classified as Mongoloid, 89% (25 of 28 patients) were Hispanic.

TABLE 8.3.2: 1 Disease Characteristics for All Treated Patients - 181

		Treatment Group				
		Placebo (N=157)	Meloxicam 3.75 mg (N=154)	Meloxicam 7.5 mg (N=154)	Meloxicam 15 mg (N=156)	Diclofenac 50 mg BID (N=153)
Target Joint	Hip	25 (15.9%)	24 (15.6%)	31 (20.1%)	25 (16.0%)	34 (22.2%)
	Knee	132 (84.1%)	130 (84.4%)	123 (79.9%)	131 (84.0%)	119 (77.8%)
Other Involved Joint		139 (88.5%)	141 (91.6%)	140 (90.9%)	138 (88.5%)	136 (88.9%)
Duration of OA (yrs.)	≤ 5 years	73 (46.5%)	73 (47.4%)	73 (47.4%)	89 (57.1%)	74 (48.4%)
	> 5 years	84 (53.5%)	81 (52.6%)	81 (52.6%)	67 (42.9%)	79 (51.6%)
	Mean ± SD	8 ± 7.2	9 ± 9.4	8 ± 8.4	7 ± 7.8	9 ± 8.3
Total duration of Prior NSAID Use (days)	N	155	154	151	155	149
	Mean ± SD	1455 ± 1590.8	1512 ± 1818.9	1404 ± 1573.1	1372 ± 1591.2	1437 ± 1753.6
Duration of Prior Diclofenac Use (days)	N	30	31	28	30	26
	Mean ± SD	514 ± 634.2	810 ± 957.1	475 ± 660.5	717 ± 927.4	763 ± 1098.8

Source: APPENDIX 15.9.2, TABLE 2.1, TABLE 3.1, and TABLE 3.3.1

DEATHS

There were a total of 95 deaths in this submission, 88 (66 on meloxicam) in the NDA and 7 (6 on meloxicam) in the 4 month Update. Deaths defined as "treatment emergent" (occurring while on treatment, within 14 days of stopping treatment, or as a result of an AE on treatment or within 14 days of stopping) yielded 58 meloxicam patients in the NDA and 6 in the Update. The table below shows these 58 deaths. The US trial #181 had one death (due to coronary insufficiency).

TABLE 8.8.7.1.1: 2 Treatment-Emergent Deaths in Clinical Trials, Postmarketing Surveillance, and Literature as of 01 July 1998

	Treatment-Emergent Deaths[1]								
	Meloxicam			Comparator[2]			Blinded drug[3]		
Source	N	n	%	N	n	%	N	n	%
Clinical trials[4]									
Included in Integrated Safety Database	16,051	15	0.09	11,951	9	0.08			
Complete, but not integrated	3808	13	0.34	1623	2	0.12	298	1	0.34
Ongoing trials	175	0	0				2509	1	0.04
Topical/ophthalmic	250	0	0	86	0	0			
Japanese[5]	1349	2	0.15	403	0	0			
TOTAL: Treatment-Emergent Deaths in Clinical Trials	21,633	30	0.14	14,063	11	0.08	2807	2	0.07
Observational surveys or PMS[6]		28							
Literature[7]		0							
TOTAL		58							

1 This table summarizes treatment-emergent deaths only (deaths occurring either during the trial; within 14 days of last dose; or >14 days after the last dose, as a result of a process that began while the patient was in the trial).

2 Comparators include study treatments administered in a meloxicam trial and compared with meloxicam, including diclofenac, piroxicam, naproxen, other NSAIDs, and placebo. The denominator for the Integrated Safety Database is for Phase 2/3 trials only (excludes comparators in Phase 1 trials because these are not summarized in the ISS).

3 Completed but not integrated Trials 107.149 and 107.190 were blinded at the time of this writing, as were all the controlled, double-blind ongoing trials.

4 Includes patients from both controlled and uncontrolled trials, as well as healthy volunteers.

5 Very little information is available for one of these deaths; the patient died 24 days after study drug discontinuation (due to recurrence of cerebral infarction), so this patient is included as an treatment-emergent deaths because it is not known if the AE process began during or within 14 days of study drug treatment. Six healthy volunteers received meloxicam and placebo. These volunteers are counted in the denominator for both the meloxicam and comparator groups.

6 PMS = postmarketing surveillance. Exposure is estimated to be [redacted] subject-years. See Section 8.8.1 for more information.

7 Deaths reported in the literature that were not previously reported in a clinical trial report.

A full patient listing by cause of death (WHOART preferred term), whether on-treatment, pre-treatment, or post-treatment is given in Appendix 1. Patient narratives for all deaths are in Appendix 2. The narrative of a particular patient in Appendix can be located by using the trial number (the 4-6 digits of the "subject identifier") and the index at the beginning of Appendix 2. The 4mo Update death narratives are the last four pages of Appendix 2.

Deaths attributed to the GI complications of perforations/ulcers/bleeds (PUBs) total 20 on meloxicam in the NDA (plus 3 in the Update), and are shown in the table and patient listing below.

TABLE 8.8.7.1.2: 1 Treatment-Emergent Deaths Attributed to PUBs in Clinical Trials, Postmarketing Surveillance, and Literature as of 01 July 1998

	Treatment-Emergent Deaths Attributed to PUB								
	Meloxicam			Comparator[1]			Blinded drug[2]		
Source	N	n	%	N	n	%	N	n	%
Clinical trials[3]									
Included in Integrated Safety Database	16,051	2	0.01	11,951	1	0.01			
Complete, but not integrated	3808	1	0.03	1623	0	0	298	0	0
Ongoing trials	175	0	0				2509	0	0
Topical/ophthalmic	250	0	0	86	0	0			
Japanese[4]	1349	0	0	403	0	0			
TOTAL: Treatment-Emergent Deaths Attributed to PUB in Clinical Trials	21,633	3	0.01	14,063	1	0.01	2807	0	0
Observational surveys or PMS[5]		17							
Literature[6]		0							
TOTAL		20							

1 Comparators include study treatments administered in a meloxicam trial and compared with meloxicam, including diclofenac, piroxicam, naproxen, other NSAIDs, and placebo. The denominator for the Integrated Safety Database is for Phase 2/3 trials only (excludes comparators in Phase 1 trials because these are not summarized in the ISS).

2 Completed but not integrated Trials 107.149 and 107.190 were blinded at the time of this writing, as were all the controlled, double-blind ongoing trials.

3 Includes patients from both controlled and uncontrolled trials, as well as healthy volunteers.

4 Six healthy volunteers received meloxicam and placebo. These volunteers are counted in the denominator for both the meloxicam and comparator groups.

5 PMS = postmarketing surveillance. Exposure is estimated to be [redacted] subject-years. See Section 8.8.1 for more information.

6 Deaths reported in the literature that were not previously reported in a clinical trial report.

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Table F.4 Listing of Subject Deaths by Timing (On-Treatment, Post-Treatment, Pre-Treatment), System-Organ Class and WHOART Preferred Term[1]
Population: All Subjects
Trials: All Phase 1 and Phase 2-3 Trials

Cutoff Date: 3-31-97

TREATMENT-EMERGENT DEATHS

Cause of Death[2] System-Organ Class	WHOART Preferred Term	Treatment	Subject Identifier[3]	Subject Source Trial Identifier[4]	Indication /Age (yrs) /Gender	Days Post Trt[5]	Duration of Therapy (days)[6]
GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER HAEMORRHAGIC HAEMATEMESIS	Meloxicam 30 mg	107.041/109/100	107.041/109/100	RA/76/F	11	76
		Meloxicam 22.5 mg	107.083/304/175	107.083/304/175	RA/75/F		129
Gastro-Intestinal System Disorders	GI Haemorrhage	Not Related	Meloxicam 22.5	107.109	105	55	RA 70 F	121	2

[1] Subject Identifier lists trial/center/subject number for the trial in which death was reported. A subject may have more than one entry in this table if the subject had more than one preferred term listed as the cause of death.
[2] Subject Source Trial Identifier lists the originating trial/center/subject number for subjects who subsequently entered follow-up trial 107.069.
[3] Days Post Trt is the number of days after the last day of treatment that death occurred.
[4] Duration of Therapy is defined as the number of days of the particular treatment that the subject received. If the subject participated in a follow-up trial, the Duration of Therapy will include the Duration of Therapy from both the source trial and the follow-up trial if the subject did not switch treatments between the source and the follow-up trial. Any gap in treatment between the source and the follow-up trial is not included in the calculation.

Trials: Postmarketing Surveillance and Observational Sources

Cutoff Date: 7-01-98

TREATMENT-EMERGENT DEATHS

Treatment	Subject Identifier[1]	Age (yrs) /Gender	Days Post Trt[2]	Duration of Therapy (days)[3]	Cause of Death[4] System-Organ Class	WHOART Preferred Term
Meloxicam 7.5 mg	98-UK-A0143	70/M	0	10	GASTRO-INTESTINAL SYSTEM DISORDERS	GI HAEMORRHAGE
					MYO ENDO PERICARDIAL & VALVE DISORDERS	CORONARY ARTERY DISORDER
	98-UK-A0167	85/M	2	.	GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER
	98-UK-03516	85/F		174	GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER PERFORATED
	97-NL-11144	74/M	1	7	GASTRO-INTESTINAL SYSTEM DISORDERS	DUODENAL ULCER HAEMORRHAGIC
	97-BL-00074	81/F	1	26	CARDIOVASCULAR DISORDERS, GENERAL	CIRCULATORY FAILURE
					GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER HAEMORRHAGIC
	96-NL-10071	95/M	1	13	GASTRO-INTESTINAL SYSTEM DISORDERS	GI HAEMORRHAGE
	97-UK-A0140	83/M	3	95	GASTRO-INTESTINAL SYSTEM DISORDERS	GI HAEMORRHAGE
Meloxicam 15 mg	97-BL-00060	75/M	12	11	GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER PERFORATED
					GASTRO-INTESTINAL SYSTEM DISORDERS	PERITONITIS
	98-ES-00109	74/M	.	.	GASTRO-INTESTINAL SYSTEM DISORDERS	ABDOMINAL PAIN
					LIVER AND BILIARY SYSTEM DISORDERS	HEPATITIS
					LIVER AND BILIARY SYSTEM DISORDERS	JAUNDICE
	98-UK-A0191	68/F			GASTRO-INTESTINAL SYSTEM DISORDERS	DUODENAL ULCER PERFORATED
					GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER HAEMPER
Meloxicam 15 mg	98-BL-00052	101/M	.	.	GASTRO-INTESTINAL SYSTEM DISORDERS	DUODENAL ULCER HAEMORRHAGIC
					GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER HAEMORRHAGIC
					VASCULAR (EXTRACARDIAC) DISORDERS	CEREBROVASCULAR DISORDER
	98-BL-00059	/M	.	.	GASTRO-INTESTINAL SYSTEM DISORDERS	GI HAEMORRHAGE
	98-FF-S1341	83/F			GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER PERFORATED
Meloxicam 15 mg	96-BR-MOV02	51/M	3	3	CARDIOVASCULAR DISORDERS, GENERAL	CIRCULATORY FAILURE
					GASTRO-INTESTINAL SYSTEM DISORDERS	GI HAEMORRHAGE
	97-ES-00005	75/F	1	1	GASTRO-INTESTINAL SYSTEM DISORDERS	GI HAEMORRHAGE
Meloxicam 30 mg	97-UK-MCA32	72/F	1	22	GASTRO-INTESTINAL SYSTEM DISORDERS	DUODENAL ULCER PERFORATED
Meloxicam 15 mg	97-BL-00037	66/F	.	.	GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER PERFORATED
					GASTRO-INTESTINAL SYSTEM DISORDERS	PERITONITIS
	97-ES-00126	85/F	.	.	CARDIOVASCULAR DISORDERS, GENERAL	CARDIAC FAILURE
					GASTRO-INTESTINAL SYSTEM DISORDERS	GASTRIC ULCER HAEMORRHAGE

[1] Treatment-emergent deaths are those resulting from adverse events which occurred during the treatment phase of the trial or within 14 days of the last dose of treatment.
[2] Cause of Death lists all adverse events with Outcome=Death, Seriousness=Fatal or Preferred Term="DEATH".
[3] Subject Identifier lists the sponsor-assigned case identification number. A subject may have more than one entry in this table if the subject had more than one preferred term listed as the cause of death.
[4] Days Post Trt is the number of days after the last day of treatment that death occurred.

Below is a list of the causes of death, by system-organ class and WHOART Preferred Term (sometimes more than one per patient) for all meloxicam or post-meloxicam deaths in the NDA and 4 month Update (21,911 patients), and in the post-marketing surveillance and observational surveys (53,660 patients). The one obvious signal is GI System with 29 patient deaths. Of these 7 were associated with the 7.5mg dose, 16 with the 15mg, 2 with the 22.5mg, 3 with the 30 mg, and one with an unknown dose. Of these 3/7, 12/16, 1/2, and 2/3 cases were considered "related" by the investigator to doses 7.5mg, 15mg, 22.5mg, and 30mg, respectively.

Body as a whole	
chest pain	1
death	3
malaise	1
sudden death	2
Cardiovascular Disorder	
cardiac failure	11
hypertension	1
GI System Disorder	
gastric ulcer	1
gastric ulcer hemorragic	5
gastric ulcer perforated	6
duodenal ulcer hemorrhage	2
duodenal ulcer perforated	2
hematemesis	1
GI hemorrhage	9
peritonitis	2
abdominal pain	1
Liver / Biliary Disorder	
hepatic failure	1
hepatitis	1
jaundice	1
Heart Rate / Rhythm Disorders	
AV block complete	1
cardiac arrest	1
ventricular fibrillation	1
Myo Endo Pericardial / Vaive Disorders	
myocardial infarction	6
angina pectoris	2
coronary artery disorder	2
death	1
Neoplasm	
carcinoma	2
malignant neoplasm	2
pulmonary carcinoma	3
lymphoma malignant	1
bone metastases	1
Resistance Mechanism Disorder	
sepsis	5
Respiratory System Disorder	
adult resp. distress syndrome	1
pneumonia	6
respiratory insufficiency	1
dyspnea	1
worsening of COPD	1
asphyxia	1
Urinary System Disorder	
acute renal failure	3
renal function abnormal	2
Vascular Disorder	
pulmonary embolist	2
CVA	8
thromboembolism	1
Musculoskeletal System Disorder	
back pain	1
Platelet, Bleeding, Clotting Disorder	
thrombocytopenia	1
purpura	1
RBC Disorder	
anemia megaloblastic	1
myeloproliferative disorder	1

SERIOUS ADVERSE EVENTS

"Serious" here is defined as any fatal or immediately life-threatening clinical experience, any permanently or severly disabling event, or any that required or prolonged inpatient hospitalization, plus congenital anomalies, cancer, and overdoses. A total of 687 meloxicam patients in the NDA and 123 in the Update experienced a treatment-emergent serious adverse event (SAE). The same conventions for treatment-emergent are used here as for deaths above. SAEs and PUB SAEs are shown in the following tables

TABLE 8.8.7.2.1: 1 Patients with Treatment-Emergent SAEs in Clinical Trials, Postmarketing Surveillance, and Literature as of 01 July 1998

	Patients Who Experienced an SAE								
	Meloxicam			Comparator[1]			Blinded drug[2]		
Source	N	n	%	N	n	%	N	n	%
Clinical trials[3]									
Included in Integrated Safety Database	16,051	338	2.1	11,951	140	1.2			
Complete, but not integrated	3808	142	3.7	1623	39	2.4	298	1	0.3
Ongoing trials	175	2	1.1				2509	16	0.6
Topical/ophthalmic	250	0	0	86	0	0			
Japanese[4]	1349	7	0.5	403	3	0.7			
TOTAL: Patients with Treatment-Emergent SAEs in Clinical Trials	21,633	489	2.3	14,063	182	1.3	2807	17	0.6
Observational surveys or PMS 5		215							
Literature		0							
TOTAL		704							

1 Comparators include study treatments administered in a meloxicam trial and compared with meloxicam, including diclofenac, piroxicam, naproxen, other NSAIDs, and placebo. The denominator for the Integrated Safety Database is for Phase 2/3 trials only (excludes comparators in Phase 1 trials because these are not summarized in the ISS).

2 Completed but not integrated Trials 107.149 and 107.190 were blinded at the time of this writing, as were all the controlled, double-blind ongoing trials.

3 Includes patients from both controlled and uncontrolled trials, as well as healthy volunteers.

4 Six healthy volunteers received meloxicam and placebo. These volunteers are counted in the denominator for both the meloxicam and comparator groups.

5 PMS = postmarketing surveillance. Exposure is estimated to be [redacted] subject-years. See Section 8.8.1 for more information.

Sources: TABLES 8.8.3.1: 1 (N denominator), E.1, E.2, E.7 (Integrated Safety Database), and TABLES G.4.5 – G.4.14 (other sources)

TABLE 8.8.7.2.1: 2 Subjects with PUB SAEs in Clinical Trials, Postmarketing Surveillance, and Literature as of 01 July 1998

Source	Subjects with PUB SAEs								
	Meloxicam			Comparator[1]			Blinded drug[2]		
	N	n	%	N	n	%	N	n	%
Clinical trials[3]									
Included in Integrated Safety Database	16,051	28	0.17	11,951	21	0.16			
Complete, but not integrated[4]	3808	8	0.21	1623	2	0.12	298	0	0
Ongoing trials	175	0	0				2509	1	0.04
Topical/ophthalmic	250	0	0	86	0	0			
Japanese[5]	1349	0	0	403	3	0.74			
TOTAL: Patients with PUB SAEs in Clinical Trials	21,633	36	0.17	14,063	26	0.18	2807	1	0.04
Observational surveys or PMS[6]		121							
Literature		0							
TOTAL		157							

1 Comparators include study treatments administered in a meloxicam trial and compared with meloxicam, including diclofenac, piroxicam, naproxen, other NSAIDs, and placebo. The denominator for the Integrated Safety Database is for Phase 2/3 trials only (excludes comparators in Phase 1 trials because these are not summarized in the ISS).

2 Completed but not integrated Trials 107.149 and 107.190 were blinded at the time of this writing, as were all the controlled, double-blind ongoing trials.

3 Includes patients from both controlled and uncontrolled trials, as well as healthy volunteers.

4 For complete information on the endoscopy trials, refer to Section 8.8.11.1.2.

5 Six healthy volunteers received meloxicam and placebo. These volunteers are counted in the denominator for both the meloxicam and comparator groups.

6 Exposure is estimated to be [redacted] subject-years. See Section 8.8.1 for more information.

Sources: TABLES 8.8.3.1: 1 (N denominators), TABLES G.2.1, G.2.2, G.2.3, and G.2.7 (Integrated Safety Database), and TABLES G.4.5 - 14 (other sources)

The narrative of the SAE reports in the Update is given in Appendix 3, a consequence of which was adding three new AEs to the sponsor's proposed label: jaundice, interstitial nephritis, and leg edema.

SAEs for all ex-US OA trials by organ system are shown below, and by specific diagnoses (WHOART term) for GI, hepatic, renal, hematologic, skin, and cardiovascular in Appendix 4.

TABLE 8.8.7.2.2:1 Incidence of Treatment-Emergent SAEs in Phase 2/3 Controlled Trials by Trial Type, Treatment Group, and System-Organ Class (Integrated Safety Database)

System-Organ Class (SOC)	[redacted]		[redacted]				Other OA Active-Controlled Studies						Placebo-Controlled Studies			
	Meloxicam N=4635		Diclofenac N=4688		Meloxicam N=4320		Piroxicam N=4336		Meloxicam N=1164		Diclofenac N=555		Piroxicam N=335		Meloxicam N=1123		Placebo N=583	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total With Any Serious Adverse Event	56	1.2	49	1.0	26	0.6	30	0.7	28	2.4	20	3.6	7	2.1	19	1.7	6	1.0
Application Site Disorders	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Body As A Whole - General Disorders	12	0.3	7	0.1	6	0.1	2	<0.1	9	0.8	4	0.7	1	0.3	0	0	1	0.2
Cardiovascular Disorders, General	6	0.1	4	<0.1	3	<0.1	4	<0.1	0	0	1	0.2	0	0	1	<0.1	1	0.2
Central & Peripheral Nervous System Disorder	6	0.1	1	<0.1	4	<0.1	3	<0.1	1	<0.1	0	0	0	0	1	<0.1	0	0
Collagen Disorders	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Endocrine Disorders	0	0	0	0	0	0	0	0	1	<0.1	0	0	0	0	0	0	0	0
Foetal Disorders[1]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastro-Intestinal System Disorders	6	0.1	11	0.2	7	0.2	11	0.3	6	0.5	3	0.5	3	0.9	5	0.4	0	0
Hearing & Vestibular Disorders	1	<0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Heart Rate & Rhythm Disorders	4	<0.1	0	0	2	<0.1	1	<0.1	1	<0.1	0	0	0	0	0	0	1	0.2
Liver & Biliary System Disorders	0	0	2	<0.1	2	<0.1	1	<0.1	0	0	1	0.2	0	0	0	0	0	0
Metabolic & Nutritional Disorders	1	<0.1	1	<0.1	0	0	0	0	0	0	0	0	0	0	1	<0.1	0	0
Musculo-Skeletal System Disorders	7	0.2	4	<0.1	4	<0.1	2	<0.1	3	0.3	3	0.5	3	0.9	3	0.3	1	0.2
Myo Endo Pericardial & Valve Disorders	5	0.1	6	0.1	3	<0.1	2	<0.1	2	0.2	1	0.2	0	0	0	0	1	0.2
Neoplasm	5	0.1	4	<0.1	1	<0.1	2	<0.1	1	<0.1	3	0.5	1	0.3	0	0	2	0.3

1 The patient (107.154/72502/68956; 41-year-old female) was reported to have had a congenital hernia which according to the WHO Dictionary is coded in the Foetal Disorders

The US trial (#181) had 9 meloxicam, 3 diclofenac, and 2 placebo-related SAEs, listed below.

TABLE 10.2.4.2: 1 Patients with Serious Adverse Events

Patient	Age/ Gender/ Race	WHOART Preferred Term(s)/ (Reported Event)	Onset Day	Duration in Days	Intensity	Drug Relation -ship	Outcome
Placebo							
3347	79/Male/ Caucasian	THROMBOSIS CORONARY/ (Occluded coronary arteries)	76	11	Severe	No	Recovered
4072	61/Male/ Caucasian	ANXIETY/ (Panic disorder)	9	9	Mild	No	Recovered
Meloxicam 3.75 mg							
3307*	73/Male/ Caucasian	ANGINA PECTORIS/ (Coronary insufficiency)	26	1	Severe	No	Fatal
3602	74/Female/ Caucasian	CHEST PAIN/ (Chest pain)	40	2	Severe	No	Recovered
Meloxicam 7.5 mg							
3250*	60/Male/ Caucasian	EPIGLOTTITIS/ (Acute epiglottitis)	14	10	Severe	No	Recovered
3313*	56/Female/ Caucasian	RENAL CALCULUS/ (Kidney stone)	65	8	Severe	No	Sequelae
3967	74/Female/ Caucasian	MYOCARDIAL INFARCTION/ (Myocardial infarction)	84	6	Severe	No	Recovered
		CHEST PAIN/ (Right-sided musculoskeletal pain in chest)	95	4	Moderate	No	Recovered
4323*	52/Female/ Caucasian	BREAST NEOPLASM MALIGNANT FEMALE/ (Right breast cancer)	1	71	Severe	No	Recovered

Meloxicam 15 mg							
3127	58/Female/ Caucasian	SYNOVITIS/ (Loosening of right knee prosthesis)	72	63	Severe	No	Recovered
3327*	65/Female/ Caucasian	GI HAEMORRHAGE/ (Acute GI bleed)	17	7	Severe	Yes	Recovered
3725*	74/Female/ Caucasian	DYSPNOEA/ (Adult respiratory distress syndrome)	30	116	Severe	No	Recovered
		PANCREATITIS/ (Pancreatitis)	29	117	Severe	No	Recovered
Diclofenac 50 mg BID							
3144*	52/Male/ Negroid	ACCIDENT HOUSEHOLD/ (Fracture left femur)	45	Ongoing	Severe	No	Sequelae
3348	49/Female/ Caucasian	BONE METASTASES/ (Recurrence of metastatic breast cancer in pelvis and hip)	65	Ongoing	Severe	No	Not Yet Recovered
3749	67/Female/ Caucasian	BASAL CELL CARCINOMA/ (Basal cell carcinoma right neck)	28	57	Moderate	No	Recovered

† Day of trial treatment on which the SAE began.
* Patient discontinued trial due to this SAE(s).
Source: APPENDIX 15.9.2, LISTING 5.2.2

For reference, a line listing of all known patients (trial patients and a much larger observational survey/poskmarketing surveillance exposure of approximately one million patient-years) with clinically important SAEs by organ system / WHOART diagnosis is given in appendix 5. The sponsors text accompanies it, in an attempt to put a perspective on this unwieldly information.

Summary: As can be seen in the above table, and in the organ specific tables in Appendix 4, this "serious adverse event" profile does not provide any signal unexpected from a nonsteroidal agent. The Observational/Post-marketing SAE information in Appendix 5 is more informative, and is consistent with unusual/rare but severe nonsteroidal toxicities, including anaphylaxis, severe skin reactions (including epidermal necrolysis and Stevens-Johnson syndrome), asthma, hypertensive crisis, pancreatitis, acute renal failure, hepatic enzyme elevation (including one case of hepatic failure and three of clinical hepatitis), and agranulocytosis.

ADVERSE EVENTS CAUSING DISCONTINUATION

Patients discontinuing for any AE, or PUB AEs, are shown below:

TABLE 8.8.7.3.1: 1 Subjects Who Discontinued a Clinical Trial Due to AEs

	Patients Who Discontinued Due to AE[1]					
	Meloxicam			Comparator[2]		
Source: Completed Clinical Trials[3]	N	n	%	N	n	%
Included in Integrated Safety Database	16,051	1218	7.6	11,951	1009	8.4
Complete, but not integrated[4]	1617	158	9.8	186	37	19.9
Topical/ophthalmic	250	6	2.4	86	10	11.6
Japanese[5]	1349	125	9.3	403	58	14.4
TOTAL	19,267	1507	7.8	12,626	1114	8.8

1 Subjects were considered to have discontinued due to an AE based on either the end of trial CRF page or the AE CRF page.

2 Comparators include study treatments administered in a meloxicam trial and compared with meloxicam, including diclofenac, piroxicam, naproxen, other NSAIDs, and placebo. The denominator for the Integrated Safety Database is for Phase 2/3 trials only (excludes comparators in Phase 1 trials because these are not summarized in the ISS).

3 Includes patients from both controlled and uncontrolled trials, as well as healthy volunteers.

4 The following trials are not included in the denominator for the reasons noted in parentheses: 107.109, 107.149, 107.164, 107.169, 107.178, 107.179, and 107.190 (no report available, therefore discontinuations due to AEs are unknown); 107.181 (trial report submitted along with the NDA; the reviewer is referred to the report for discontinuations due to AEs); 107.065, 107.092, 107.105, and 107.111 (endoscopy trials: subjects were discontinued based on endoscopy results and not clinical symptoms). Endoscopy trials are discussed in Section 8.8.11.1.2.

5 Six healthy volunteers received meloxicam and placebo. These volunteers are counted in both the meloxicam and comparator groups.

TABLE 8.8.7.3.1: 2 Patients Who Discontinued a Clinical Trial Due to a PUB AE

	Patients Who Discontinued Due to a PUB AE[1]					
	Meloxicam			Comparator[2]		
Source: Completed Clinical Trials[3]	N	n	%	N	n	%
Included in Integrated Safety Database	16,051	41	0.25	11,951	31	0.26
Complete, but not integrated[4]	1617	12	0.74	186	8	4.30
Topical/ophthalmic	250	0	0.00	86	0	0.00
Japanese[5]	1349	2	0.10	403	2	0.50
TOTAL	19,267	55	0.30	12,626	41	0.32

1 Patients were considered to have discontinued due to an AE based on either the end of trial CRF page or the AE CRF page.

2 Comparators include study treatments administered in a meloxicam trial and compared with meloxicam, including diclofenac, piroxicam, naproxen, other NSAIDs, and placebo. The denominator for the Integrated Safety Database is for Phase 2/3 trials only (excludes comparators in Phase 1 trials because these are not summarized in the ISS).

3 Includes patients from both controlled and uncontrolled trials, as well as healthy volunteers.

4 The following trials are not included in the denominator for the reasons noted in parentheses: 107.109, 107.149, 107.164, 107.169, 107.178, 107.179, and 107.190 (no report available, therefore discontinuations due to AEs are unknown); 107.181 (trial report submitted along with the NDA; the reviewer is referred to the report for discontinuations due to AEs); 107.065, 107.092, 107.105, and 107.111 (endoscopy trials: subjects were discontinued based on endoscopy results and not clinical symptoms). Endoscopy trials are discussed in detail in Section 8.8.11.1.2.

5 Six healthy volunteers received meloxicam and placebo. These volunteers are counted in both the meloxicam and comparator groups.

Using the same format as used for SAEs, AEs causing discontinuation are shown in the organ system table below, and in the diagnosis (WHOART term) table for selected systems in Appendix 6.

TABLE 8.8.7.3.2: 1 Incidence of AEs Leading to Discontinuation in Phase 2/3 Controlled Trials by Trial Type, Treatment Group, and System-Organ Class (Integrated Safety Database)

System-Organ Class (SOC)	[redacted]				[redacted]				Other OA Active-Controlled Studies						Placebo-Controlled Studies			
	Meloxicam N=4635		Diclofenac N=4688		Meloxicam N=4320		Piroxicam N=4336		Meloxicam N=1164		Diclofenac N=555		Piroxicam N=335		Meloxicam N=1123		Placebo N=583	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total With Any Adverse Event Leading to Discontinuation	257	5.5	378	8.1	270	6.3	322	7.4	146	12.5	89	16.0	44	13.1	77	6.9	33	5.7
Application Site Disorders	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Body As A Whole - General Disorders	34	0.7	33	0.7	33	0.8	38	0.9	29	2.5	16	2.9	3	0.9	9	0.8	3	0.5
Cardiovascular Disorders, General	10	0.2	6	0.1	8	0.2	9	0.2	3	0.3	0	0	1	0.3	1	<0.1	1	0.2
Central & Peripheral Nervous System Disorder	67	1.4	43	0.9	42	1.0	40	0.9	25	2.1	8	1.4	3	0.9	11	1.0	11	1.9
Collagen Disorders	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Endocrine Disorders	0	0	0	0	0	0	0	0	1	<0.1	0	0	0	0	0	0	0	0
Facial Disorders	0	0	0	0	0	0	1	<0.1	0	0	0	0	0	0	0	0	0	0
Gastro-Intestinal System Disorders	131	2.8	287	6.1	156	3.6	224	5.2	95	8.2	51	9.2	34	10.1	43	3.8	14	2.4
Hearing & Vestibular Disorders	3	<0.1	1	<0.1	1	<0.1	1	<0.1	0	0	0	0	0	0	2	0.2	0	0
Heart Rate & Rhythm Disorders	11	0.2	7	0.1	6	0.1	5	0.1	3	0.3	1	0.2	0	0	0	0	2	0.3
Liver & Biliary System Disorders	0	0	1	<0.1	2	<0.1	4	<0.1	1	<0.1	5	0.9	0	0	3	0.3	0	0
Metabolic & Nutritional Disorders	3	<0.1	1	<0.1	1	<0.1	1	<0.1	1	<0.1	0	0	0	0	1	<0.1	0	0
Musculo-Skeletal System Disorders	20	0.4	16	0.3	31	0.7	12	0.3	9	0.8	11	2.0	1	0.3	6	0.5	4	0.7
Myo Endo Pericardial & Valve Disorders	2	<0.1	3	<0.1	1	<0.1	2	<0.1	2	0.2	1	0.2	1	0.3	1	<0.1	2	0.3
Neoplasm	1	<0.1	1	<0.1	0	0	4	<0.1	1	<0.1	2	0.4	1	0.3	0	0	1	0.2
Platelet, Bleeding & Clotting Disorders	1	<0.1	2	<0.1	8	0.2	2	<0.1	1	<0.1	1	0.2	0	0	0	0	0	0
Psychiatric Disorders	10	0.2	12	0.3	17	0.4	19	0.4	8	0.7	3	0.5	1	0.3	2	0.2	0	0
Red Blood Cell Disorders	0	0	1	<0.1	0	0	0	0	2	0.2	0	0	1	0.3	1	<0.1	0	0
Reproductive Disorders, Female	0	0	2	<0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reproductive Disorders, Male	1	<0.1	0	0	0	0	0	0	0	0	0	0	0	0	1	<0.1	0	0
Resistance Mechanism Disorders	2	<0.1	0	0	1	<0.1	5	0.1	0	0	1	0.2	0	0	1	<0.1	1	0.2
Respiratory System Disorders	13	0.3	13	0.3	9	0.2	9	0.2	1	<0.1	3	0.5	1	0.3	2	0.2	1	0.2
Secondary Terms	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin & Appendages Disorders	23	0.5	23	0.5	22	0.5	13	0.3	9	0.8	7	1.3	2	0.6	10	0.9	2	0.3
Special Senses Other, Disorders	0	0	1	<0.1	1	<0.1	1	<0.1	1	<0.1	0	0	0	0	0	0	0	0
Urinary System Disorders	9	0.2	7	0.1	4	<0.1	7	0.2	8	0.7	1	0.2	2	0.6	3	0.3	1	0.2
Vascular (Extracardiac) Disorders	3	<0.1	6	0.1	2	<0.1	3	<0.1	2	0.2	2	0.4	0	0	0	0	0	0
Vision Disorders	2	<0.1	0	0	3	<0.1	3	<0.1	1	<0.1	0	0	0	0	2	0.2	0	0
White Cell & Resistance Disorders	0	0	0	0	1	<0.1	1	<0.1	1	<0.1	0	0	1	0.3	0	0	0	0
Discontinuation Due to AE Noted on the End Of Trial Page, But No AE Reported	5	0.1	1	<0.1	2	<0.1	5	0.1	2	0.2	1	0.2	1	0.3	0	0	1	0.2

US trial #181 had 56 patients with an AE leading to discontinuation. These are shown below.

TABLE 10.2.4.3: 1 Summary of the Incidence of Discontinuations Due to Adverse Events for All Treated Patients

	Treatment at Onset				
	Placebo	Meloxicam 3.75 mg	Meloxicam 7.5 mg	Meloxicam 15 mg	Diclofenac 50 mg BID
	(N=157)	(N=154)	(N=154)	(N=156)	(N=153)
Patients Discontinued due to AE	6 (3.8%)	13 (8.4%)	11 (7.1%)	13 (8.3%)	13 (8.5%)
Patients with GI Event	2 (1.3%)	5 (3.2%)	5 (3.2%)	6 (3.8%)	7 (4.6%)
AE Discontinuation Information by Patient*					
Drug Related	4	7	6	8	10
Severe	1	4	8	4	3
Moderate	4	8	2	7	8
Mild	1	1	1	2	2
Onset 1-14 days	2	10	5	5	7
15-28 days	2	1	4	4	3
29-56 days	0	2	1	3	2
≥57 days	2	0	1	1	1

Four patients (Patients 3203 and 4322 who were randomized to receive placebo and Patients 3379 and 4254 who were randomized to receive meloxicam 15 mg) discontinued due to AEs which started during the screening period. These patients are not included in this table.

* Patients may have had multiple events leading to discontinuation. In such cases, for tabular and discussion purposes, the event with the earliest onset and the event with the most severe intensity and causality are summarized.

Summary: Although a sparse database (small denominators throughout), it mimics the conclusions from the earlier analyses.

ALL TREATMENT-EMERGENT AEs

Treatment-emergent AEs are displayed below by organ system, and by those (WHOART) diagnoses with an incidence of at least 1% in at least one treatment group. The full list AEs by diagnoses for the same selected organ systems (GI, hep, renal, hem, skin, CV) is Appendix 7.

TABLE 8.8.7.4.2: 1 Incidence of Treatment-Emergent AEs in Phase 2/3 Controlled Trials by Trial Type, Treatment Group, and System-Organ Class (Integrated Safety Database)

System Organ Class (SOC)	[redacted]				[redacted]				Other OA Active-Controlled Studies						Placebo-Controlled Studies			
	Meloxicam N=4635		Diclofenac N=4688		Meloxicam N=4320		Piroxicam N=4336		Meloxicam N=1164		Diclofenac N=555		Piroxicam N=315		Meloxicam N=1123		Placebo N=583	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total with Any Treatment-Emergent Adverse Event	1268	27.4	1496	31.9	969	22.4	1203	27.7	495	42.5	238	42.9	151	45.1	402	35.8	188	32.2
Application Site Disorders	0	0	0	0	0	0	0	0	1	<0.1	0	0	0	0	2	0.2	2	0.3
Body As A Whole - General Disorders	157	3.4	171	3.6	156	3.6	210	4.8	99	8.5	39	7.0	12	3.6	69	6.1	25	4.3
Cardiovascular Disorders, General	27	0.6	23	0.5	26	0.6	40	0.9	15	1.3	5	0.9	5	1.5	11	1.0	2	0.3
Central & Peripheral Nervous System Disorders	235	5.1	215	4.6	158	3.7	150	3.5	79	6.8	36	6.5	18	5.4	81	7.2	51	8.7
Collagen Disorders	0	0	1	<0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Endocrine Disorders	1	<0.1	0	0	1	<0.1	0	0	2	0.2	1	0.2	0	0	0	0	0	0
Foetal Disorders[1]	0	0	0	0	0	0	1	<0.1	0	0	0	0	0	0	0	0	0	0
Gastro-Intestinal System Disorders	616	13.3	881	18.8	445	10.3	665	15.3	239	20.5	128	23.1	84	25.1	194	17.3	70	12
Hearing & Vestibular Disorders	6	0.1	9	0.2	7	0.2	11	0.3	7	0.6	2	0.4	0	0	5	0.4	2	0.3
Heart Rate & Rhythm Disorders	17	0.4	21	0.4	17	0.4	10	0.2	4	0.3	1	0.2	3	0.9	2	0.2	4	0.7
Liver & Biliary System Disorders	12	0.3	28	0.6	7	0.2	13	0.3	7	0.6	8	1.4	0	0	7	0.6	1	0.2
Metabolic & Nutritional Disorders	12	0.3	10	0.2	5	0.1	11	0.3	16	1.4	4	0.7	2	0.6	9	0.8	3	0.5
Musculo-Skeletal System Disorders	97	2.1	93	2.0	108	2.5	79	1.8	43	3.7	25	4.5	6	1.8	67	6.0	38	6.5
Myo Endo Pericardial & Valve Disorders	8	0.2	8	0.2	7	0.2	5	0.1	5	0.4	2	0.4	1	0.3	4	0.4	2	0.3
Neoplasm	7	0.2	4	<0.1	2	<0.1	6	0.1	1	<0.1	3	0.5	1	0.3	0	0	2	0.3
Platelet, Bleeding & Clotting Disorders	15	0.3	17	0.4	17	0.4	17	0.4	7	0.6	3	0.5	0	0	2	0.2	2	0.3
Psychiatric Disorders	71	1.5	70	1.5	56	1.3	55	1.3	36	3.1	12	2.2	10	3.0	25	2.2	14	2.4
Red Blood Cell Disorders	8	0.2	13	0.3	6	0.1	6	0.1	16	1.4	4	0.7	7	2.1	6	0.5	0	0
Reproductive Disorders, Female	10	0.2	8	0.2	6	0.1	6	0.1	4	0.3	2	0.4	0	0	6	0.5	1	0.2
Reproductive Disorders, Male	3	<0.1	2	<0.1	3	<0.1	4	<0.1	4	0.3	0	0	0	0	2	0.2	0	0
Resistance Mechanism Disorders	24	0.5	19	0.4	18	0.4	28	0.5	16	1.4	7	1.3	8	2.4	12	1.1	5	0.9
Respiratory System Disorders	145	3.1	155	3.3	86	2.0	92	2.1	72	6.2	25	4.5	19	5.7	49	4.4	15	2.6
Secondary Terms	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin & Appendages Disorders	101	2.2	87	1.9	72	1.7	69	1.6	54	4.6	21	3.8	11	3.3	52	4.6	13	2.2
Special Senses Other, Disorders	5	0.1	9	0.1	4	<0.1	9	0.2	2	0.2	1	0.2	1	0.3	0	0	0	0
Urinary System Disorders	64	1.4	83	1.7	42	1.0	72	1.7	59	5.1	13	2.3	18	5.4	22	2.0	9	1.5
Vascular (Extracardiac) Disorders	13	0.3	18	0.4	10	0.2	11	0.3	8	0.7	6	1.1	1	0.3	2	0.2	0	0
Vision Disorders	33	0.7	18	0.4	21	0.5	23	0.5	10	0.9	5	0.9	5	1.5	19	1.7	6	1.0
White Cell & RES Disorders	12	0.3	11	0.2	5	0.1	7	0.2	5	0.4	0	0	2	0.6	3	0.3	2	0.3

1 The patient (107.154/72502/68956; 41-year-old female) was reported to have had a congenital hernia which according to the WHO Dictionary is coded in the Foetal Disorders Category.

TABLE 8.8.7.4.2: 2 Treatment-Emergent AEs with an Incidence of ≥1% in At Least One Treatment Group in Phase 2/3 Controlled Trials by Trial Type, Treatment Group, System-Organ Class, and Preferred Term (Integrated Safety Database)

System Organ Class (SOC) WHOART Preferred Term	[redacted]		[redacted]		Other OA Active-Controlled Studies						Placebo-Controlled Studies			
	Meloxicam N=4635		Diclofenac N=4688		Meloxicam N=4320		Piroxicam N=4336		Meloxicam N=1164		Diclofenac N=555		Piroxicam N=335		Meloxicam N=1123		Placebo N=583	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Body As A Whole - General Disorders																		
Pain	37	0.8	39	0.8	40	0.9	37	0.9	28	2.4	7	1.3	1	0.3	4	0.4	6	1.0
Fatigue	24	0.5	29	0.6	26	0.6	25	0.6	13	1.1	6	1.1	3	0.9	17	1.5	6	1.0
Influenza-like symptoms	0	0	0	0	14	0.3	13	0.3	13	1.1	6	1.1	1	0.3	17	1.5	6	1.0
Malaise	11	0.2	15	0.3	9	0.2	16	0.4	8	0.7	6	1.1	1	0.3	2	0.2	0	0
Cardiovascular Disorders, General																		
Hypertension	12	0.3	14	0.3	10	0.2	18	0.4	12	1.0	4	0.7	4	1.2	8	0.7	1	0.2
Central & Peripheral Nervous System Disorders																		
Headache	128	2.8	108	2.3	83	1.9	69	1.6	26	2.2	7	1.3	4	1.2	47	4.2	30	5.1
Dizziness	64	1.4	54	1.2	32	0.7	47	1.1	22	1.9	11	2.0	9	2.7	16	1.4	10	1.7
Cramps Legs	13	0.3	21	0.4	10	0.2	7	0.2	7	0.6	6	1.1	3	0.9	2	0.2	0	0
Vertigo	16	0.3	15	0.3	18	0.4	9	0.2	5	0.4	6	1.1	0	0	9	0.8	8	1.4
Gastro-Intestinal System Disorders																		
Abdominal Pain	150	3.2	262	5.6	89	2.1	131	3.5	35	3.0	32	5.8	25	7.5	34	3.0	14	2.4
Constipation	44	0.9	43	0.9	26	0.6	49	1.1	17	1.5	6	1.1	8	2.4	5	0.4	2	0.3
Diarrhoea	100	2.2	194	4.1	70	1.6	79	1.8	27	2.3	25	4.5	16	4.8	32	2.8	21	3.6
Dyspepsia	190	4.1	269	5.7	146	3.4	243	5.6	99	8.5	48	8.6	29	8.7	65	5.8	22	3.8
Flatulence	25	0.5	57	1.2	18	0.4	32	0.7	18	1.5	7	1.3	3	0.9	10	0.9	3	0.5
Nausea	121	2.6	152	3.2	92	2.1	131	3.0	56	4.8	20	3.6	10	3.0	43	3.8	13	2.2
Vomiting	26	0.6	36	0.8	29	0.7	30	0.7	16	1.4	11	2.0	1	0.3	11	1.0	4	0.7
Musculo-Skeletal System Disorders																		
Arthralgia	30	0.6	28	0.6	18	0.4	12	0.3	17	1.5	10	1.8	0	0	21	1.9	12	2.1
Arthritis Aggravated	17	0.4	20	0.4	46	1.1	18	0.4	0	0	0	0	0	0	4	0.4	1	0.2
Back Pain	30	0.6	16	0.3	17	0.4	18	0.4	15	1.3	5	0.9	4	1.2	18	1.6	13	2.2
Spondylitis Ankylosing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0.3	6	1.0
Psychiatric Disorders																		
Insomnia	17	0.4	19	0.4	15	0.3	9	0.2	15	1.3	2	0.4	3	0.9	8	0.7	1	0.2
Somnolence	26	0.6	18	0.4	14	0.3	15	0.3	10	0.9	3	0.5	2	0.6	8	0.7	8	1.4
Red Blood Cell Disorders																		
Anaemia	4	<0.1	6	0.1	2	<0.1	6	0.1	16	1.4	2	0.4	6	1.8	6	0.5	0	0
Respiratory System Disorders																		
Rhinitis	67	1.4	68	1.5	9	0.2	10	0.2	7.6	0.6	3	0.5	0	0	2	0.2	2	0.3
Bronchitis	26	0.6	32	0.7	19	0.4	16	0.4	10	0.9	2	0.4	1	0.3	17	1.5	2	0.3
Pharyngitis	19	0.4	26	0.6	10	0.2	14	0.3	8	0.7	3	0.5	4	1.2	11	1.0	3	0.5
Upper Respiratory Tract Infection	9	0	1	<0.1	18	0.4	25	0.6	36	3.3	7	1.3	11	3.3	11	1.0	1	0.2
Skin & Appendages Disorders																		
Pruritus	16	0.3	9	0.2	23	0.5	6	0.1	10	0.9	4	0.7	0	0	20	1.8	5	0.9
Rash	2	<0.1	3	<0.1	16	0.4	11	0.3	10	0.9	5	0.9	3	0.9	13	1.2	4	0.7
Urinary System Disorders																		
Urinary Tract Infection	21	0.5	14	0.3	10	0.2	11	0.3	32	2.7	9	1.6	11	3.3	7	0.6	4	0.7

Sources: TABLES L1.6, L1.5, and L1.3

These tables show the following AEs, in addition to GI events, that show a rate greater than placebo.

TABLE 8.8.7.4.3: 7 Selected AEs (Other than GI) with an Incidence Greater in Meloxicam-Treated Patients Compared to Placebo - Phase 2/3 Controlled Studies (Integrated Safety Database)

WHOART Preferred Term	Meloxicam N=1123	Placebo N=583
	n (%)	n (%)
Hepatic Enzymes Increased	7 (0.6)	0
NPN Increased	2 (0.2)	0
Anaemia	6 (0.5)	0
Marrow Depression	0	0
Pruritus	20 (1.8)	5 (0.9)
Rash	13 (1.2)	4 (0.7)
Hypertension	8 (0.7)	1 (0.2)
Oedema	6 (0.5)	1 (0.2)
Oedema Peripheral	8 (0.7)	0
Weight Increase	1 (<0.1)	0

Source: TABLE I.2.3

These AEs are also analyzed by severity, by relation to drug, and by outcome, shown in the following.

TABLE 8.8.7.4.5: 1 Number of Meloxicam-Treated Patients with AEs by Severity in Phase 2/3 Trials (Integrated Safety Database)

System-Organ Class	Meloxicam (all doses)									
	Patients (n, %) Who Had an AE in the Specified System Organ Class (N = n from Total column)								Total (N=15456)	
	Severe		Moderate		Mild		Unknown			
	n	%	n	%	n	%	n	%	n	%
Total with Any Adverse Event	889	17.3	2389	43.1	1940	37.8	88	1.7	5126	33.2
Application Site Disorders	0	0	4	44.4	4	44.4	1	11.1	9	<0.1
Body as a Whole, General Disorders	115	12.6	397	43.6	384	42.2	14	1.5	910	5.9
Cardiovascular Disorders, General	20	12.3	63	39.1	72	44.7	6	3.7	161	1.0
Central & Peripheral Nervous System Disorders	131	14.1	395	42.6	391	42.2	10	1.1	927	6.0
Collagen Disorders	1	33.3	0	0	1	33.3	1	33.3	3	<0.1
Endocrine Disorders	5	25.0	5	25.0	8	40.0	2	10.0	20	0.1
Gastro-Intestinal System Disorders	277	11.3	1004	41.0	1144	46.7	24	1.0	2449	15.8
Hearing and Vestibular Disorders	0	0	17	38.6	26	59.1	1	2.3	44	0.3
Heart Rate and Rhythm Disorders	12	14.5	29	34.9	40	48.2	2	2.4	83	0.5
Liver and Biliary System Disorders	10	10.4	31	32.3	52	54.2	3	3.1	96	0.6
Metabolic and Nutritional Disorders	9	10.1	30	33.7	46	51.7	4	4.5	89	0.6
Musculo-Skeletal System Disorders	230	34.6	289	43.5	127	19.1	19	2.9	665	4.3
Myo Endo Pericardial & Valve Disorders	13	25.0	20	38.5	17	32.7	2	3.8	52	0.3
Neoplasm	7	24.1	11	37.9	7	24.1	4	13.8	29	0.2
Platelet, Bleeding & Clotting Disorders	9	11.4	27	34.2	42	53.2	1	1.3	79	0.5
Psychiatric Disorders	31	9.8	117	36.9	165	52.1	4	1.3	317	2.1
Red Blood Cell Disorders	6	7.1	25	29.8	51	60.7	2	2.4	84	0.5
Reproductive Disorders, Female	6	12.2	25	51.0	17	34.7	1	2.0	49	0.3
Reproductive Disorders, Male	6	30.0	8	40.0	6	30.0	0	0	20	0.1
Resistance Mechanism Disorders	28	13.5	98	47.3	73	35.3	8	3.9	207	1.3
Respiratory System Disorders	53	8.2	301	46.7	282	43.7	8	1.2	644	4.2
Skin and Appendages Disorders	52	8.2	217	34.4	356	56.4	6	1.0	631	4.1
Special Senses Other, Disorders	0	0	8	32.1	13	61.9	0	0	21	0.1
Urinary System Disorders	23	5.5	134	32.1	216	51.7	45	10.8	418	2.7
Vascular (Extracardiac) Disorders	13	17.3	31	41.3	30	40.0	1	1.3	75	0.5
Vision Disorders	18	11.2	49	30.4	93	57.8	1	0.6	161	1.0
White Cell and RES Disorders	0	0	16	37.2	23	53.5	4	9.3	43	0.3

TABLE 8.8.7.4.6: 1 Number of Meloxicam-Treated Patients with AEs by Relationship to Study Drug in Phase 2/3 Studies (Integrated Safety Database)

System-Organ Class	Meloxicam							
	Patients (n, %) Who Had an AE in the Specified System-Organ Class (N = n from Total column)						Total (N=1545	
	Related		Not Related		Unknown			
	n	%	n	%	n	%	n	%
Total with Any Adverse Event	2952	57.6	1917	37.4	257	5.0	5126	33.2
Application Site Disorders	5	55.6	3	33.3	1	11.1	9	<0.1
Body as a Whole, General Disorders	344	37.8	524	57.6	42	4.6	910	5.9
Cardiovascular Disorders, General	57	35.4	94	58.4	10	6.2	161	1.0
Central & Peripheral Nervous System Disorders	503	54.3	378	40.8	46	5	927	6.0
Collagen Disorders	2	66.7	1	33.3	0	0	3	<0.1
Endocrine Disorders	2	10.0	16	80.0	2	10.0	20	0.1
Gastro-Intestinal System Disorders	1806	77.0	458	18.7	105	4.3	2449	15.8
Hearing and Vestibular Disorders	11	25.0	32	72.7	1	2.3	44	0.3
Heart Rate and Rhythm Disorders	26	31.3	56	67.5	1	1.2	83	0.5
Liver and Biliary System Disorders	60	62.5	32	33.3	4	4.2	96	0.6
Metabolic and Nutritional Disorders	22	24.7	64	71.9	3	3.4	89	0.6
Musculo-Skeletal System Disorders	120	18.0	514	77.3	31	4.7	665	4.3
Myo Endo Pericardial & Valve Disorders	4	7.7	45	86.5	3	5.8	52	0.3
Neoplasm	2	6.9	26	89.7	1	3.4	29	0.2
Platelet, Bleeding & Clotting Disorders	34	43.0	43	54.4	2	2.5	79	0.5
Psychiatric Disorders	149	47.8	156	49.2	12	3.8	317	2.1
Red Blood Cell Disorders	37	44.0	44	52.4	3	3.6	84	0.5
Reproductive Disorders, Female	5	10.2	42	85.7	2	4.1	49	0.3
Reproductive Disorders, Male	2	10.0	17	85.0	1	5.0	20	0.1
Resistance Mechanism Disorders	15	7.2	179	86.5	13	6.3	207	1.3
Respiratory System Disorders	59	9.2	562	87.3	23	3.6	644	4.2
Skin and Appendages Disorders	340	53.9	257	40.7	34	5.4	631	4.1
Special Senses Other, Disorders	19	90.5	2	9.5	0	0	21	0.1
Urinary System Disorders	99	23.7	264	63.2	55	13.2	418	2.7
Vascular (Extracardiac) Disorders	24	32.0	51	68.0	0	0	75	0.5
Vision Disorders	38	23.6	119	73.9	4	2.5	161	1.0
White Cell and RES Disorders	23	53.5	16	37.2	4	9.3	43	0.3

Note: Percentages for the three relatedness columns were calculated using the Total 'n' for each respective system-organ class as the denominator, while t [illegible] ('n' (the number of meloxicam-treated patients in Phase 2/3 and

TABLE 8.8.7.4.7: 1 Number of Meloxicam-Treated Patients with AEs by Outcome in Phase 2/3 Studies (Integrated Safety Database)

System-Organ Class	Meloxicam											
	Patients (n, %) Who Had an AE in the Specified System-Organ Class (N = n from Total column)										Total (N=15456)	
	Death		Not Resolved		Resolved with Seq.		Resolved		Unknown			
	n	%	n	%	n	%	n	%	n	%	n	%
Total with Any Adverse Event	15	0.3	1169	22.8	39	0.8	3757	73.3	146	2.8	5126	33.2
Application Site Disorders	0	0	1	11.1	0	0	7	77.8	1	11.1	9	<0.1
Body as a Whole, General Disorders	3	0.3	165	18.1	7	0.8	697	76.6	38	4.2	910	5.9
Cardiovascular Disorders, General	0	0	48	29.8	0	0	104	64.6	9	5.6	161	1.0
Central & Peripheral Nervous System Disorders	0	0	117	12.6	5	0.5	783	84.5	22	2.4	927	6.0
Collagen Disorders	0	0	0	0	0	0	2	66.7	1	33.3	3	<0.1
Endocrine Disorders	0	0	9	45.0	1	5.0	6	30.0	4	20.0	20	0.1
Gastro-Intestinal System Disorders	2	0.1	296	12.1	11	0.4	2082	85.0	58	2.4	2449	15.8
Hearing and Vestibular Disorders	0	0	9	20.5	0	0	34	77.3	1	2.3	44	0.3
Heart Rate and Rhythm Disorders	2	2.4	14	16.9	0	0	63	75.9	4	4.8	83	0.5
Liver and Biliary System Disorders	0	0	28	29.2	1	1.0	57	59.4	10	10.4	96	0.6
Metabolic and Nutritional Disorders	0	0	37	41.6	0	0	49	55.1	3	3.4	89	0.6
Musculo-Skeletal System Disorders	1	0.2	222	33.4	8	1.2	405	60.9	29	4.4	665	4.3
Myo Endo Pericardial & Valve Disorders	3	5.8	11	21.2	4	7.7	32	61.5	2	3.8	52	0.3
Neoplasm	1	3.4	11	37.9	0	0	14	48.3	3	10.3	29	0.2
Platelet, Bleeding & Clotting Disorders	0	0	13	16.5	1	1.3	62	78.5	3	3.8	79	0.5
Psychiatric Disorders	0	0	72	22.7	1	0.3	239	75.4	5	1.6	317	2.1
Red Blood Cell Disorders	0	0	33	39.3	2	2.4	42	50.0	7	8.3	84	0.5
Reproductive Disorders, Female	0	0	10	20.4	0	0	39	79.6	0	0	49	0.3
Reproductive Disorders, Male	0	0	5	25.0	0	0	14	70.0	1	5.0	20	0.1
Resistance Mechanism Disorders	1	0.5	27	13.0	1	0.5	171	82.6	7	3.4	207	1.3
Respiratory System Disorders	4	0.6	78	12.1	2	0.3	550	85.4	10	1.6	644	4.2
Skin and Appendages Disorders	0	0	130	20.6	3	0.5	474	75.1	24	3.8	631	4.1

Source: TABLE 1.5

TTS trial #181 showed the following AEs by organ system (below) and by diagnosis (appendix 8).

TABLE 10.2.3: 1 Incidence of Adverse Events (≥ 2% in the All Meloxicam Group) by Treatment at Onset and WHO System-Organ Class (All Treated Patients)

	Treatment at Onset					
System Organ Class	Placebo (N=157)	Meloxicam 3.75 mg (N=154)	Meloxicam 7.5 mg (N=154)	Meloxicam 15 mg (N=156)	All Meloxicam (N=464)	Diclofenac 50 mg BID (N=153)
Patients with any AE	75 (47.8%)	90 (58.4%)	86 (55.8%)	90 (57.7%)	266 (57.3%)	101 (66.0%)
Body As A Whole	26 (16.6%)	33 (21.4%)	30 (19.5%)	23 (14.7%)	86 (18.5%)	29 (19.0%)
Central and Periph. Nervous System	22 (14.0%)	24 (15.6%)	19 (12.3%)	28 (17.9%)	71 (15.3%)	16 (10.5%)
Gastrointestinal System	27 (17.2%)	30 (19.5%)	31 (20.1%)	27 (17.3%)	88 (19.0%)	43 (28.1%)
Musculoskeletal System	12 (7.6%)	14 (9.1%)	9 (5.8%)	12 (7.7%)	35 (7.5%)	5 (3.3%)
Psychiatric	3 (1.9%)	3 (1.9%)	3 (1.9%)	9 (5.8%)	15 (3.2%)	6 (3.9%)
Resistance Mechanism	2 (1.3%)	5 (3.2%)	5 (3.2%)	3 (1.9%)	13 (2.8%)	7 (4.6%)
Respiratory System	17 (10.8%)	15 (9.7%)	11 (7.1%)	16 (10.3%	42 (9.1%)	23 (15.0%)
Skin and Appendages	7 (4.5%)	8 (5.2%)	8 (5.2%)	6 (3.8%)	22 (4.7%)	4 (2.6%)
Urinary System	6 (3.8%)	3 (1.9%)	5 (3.2%)	6 (3.8%)	14 (3.0%)	4 (2.6%)

Denominators for percentages are the total number of patients treated in each treatment group.
Source: APPENDIX 15.9.2, TABLE 5.2.2.

Summary: This database reflects what has been noted earlier in this review for more severe reactions, and it closely mimics what one expects for the non-serious toxicity profile for nonsteroidals.

IS THERE A TOXICITY-DOSE EFFECT?

The breakdown of treatment-emergent SAEs and treatment-emergent AEs leading to discontinuation by dose is shown below:

TABLE 8.8.7.2.2: 2 Incidence of Treatment-Emergent SAEs by Treatment Group in Controlled Phase 2/3 Trials (Integrated Safety Database)

Treatment	Mean Exposure (days)		Event		Cumulative Probability of First SAE		
	Mean	n[1]	n[2]	%	Day 21	Day 84[3]	Day 168[3]
Meloxicam 7.5 mg (N=9737)	31.78	9730	95	1.0	0.006	0.039	0.058
Meloxicam 15 mg (N=2442)	65.99	2435	52	2.1	0.009	0.037	0.051
Meloxicam 22.5 mg (N=338)	144.82	337	16	4.7	0.000	0.056	0.056
Meloxicam 30 mg (N=707)	28.46	707	10	1.4	0.014	0.042	-
Meloxicam > 30 mg (N=98)	20.26	98	3	3.1	0.033	-	-
Meloxicam (All Doses) (N=13322)	40.64	13307	176	1.3	0.007	0.040	0.053
Diclofenac SR (N=5431)	31.34	5429	69	1.3	0.007	0.040	0.060
Piroxicam (N=5641)	39.42	5635	51	0.9	0.004	0.030	0.048
Naproxen (N=243)	116.53	243	11	4.5	0.013	0.034	0.057
Placebo (N=583)	41.88	580	6	1.0	0.009	0.023	0.023

[1] Only subjects with exposure data are included.
[2] Only subjects with time to event are included.
[3] Insufficient numbers of subjects remained on treatment beyond 84 days at the 30 mg dose and beyond 21 days at the >30 mg doses for probabilities to be calculated for those time periods.
Source: TABLE K.7.1.3

TABLE 8.8.7.3.2: 2 Incidence of Treatment-Emergent AEs Leading to Discontinuation by Treatment Group in Controlled Phase 2/3 Trials (Integrated Safety Database)

Treatment	Mean Exposure (days)		Event		Cumulative Probability of First AE That Led to Discontinuation		
	Mean	n[1]	n[2]	%	Day 21	Day 84[3]	Day 168[3]
Meloxicam 7.5 mg (N=9737)	31.78	9730	584	6.0	0.053	0.076	0.084
Meloxicam 15 mg (N=2442)	65.99	2435	211	8.6	0.068	0.122	0.134
Meloxicam 22.5 mg (N=338)	144.82	337	45	13.3	0.073	0.122	0.141
Meloxicam 30 mg (N=707)	28.46	707	55	7.8	0.080	0.139	-
Meloxicam > 30 mg (N=98)	20.26	98	11	11.2	0.113	-	-
Meloxicam (All Doses) (N=13322)	40.64	13307	906	6.8	0.058	0.097	0.108
Diclofenac SR (N=5431)	31.34	5429	467	8.6	0.077	0.100	0.134
Piroxicam (N=5641)	39.42	5635	458	8.1	0.066	0.119	0.128
Naproxen (N=243)	116.53	243	39	16.0	0.118	0.151	0.179
Placebo (N=583)	41.88	580	31	5.3	0.057	0.083	0.083

[1] Only subjects with exposure data are included.
[2] Only subjects with time to event are included.
[3] Insufficient numbers of subjects remained on treatment beyond 84 days at the 30 mg dose and beyond 21 days at the >30 mg doses for probabilities to be calculated for those time periods.
Source: TABLE K.7.1.5

Analysis of the cumulative probability of GI events in the controlled OA t al database (excluding the large trials using 7.5mg: #153 and #154), make the dose effect more obvious, as shown in the table below.

TABLE K.6 All Gastrointestinal Events: Comparison of Controlled and Uncontrolled Trials

Population: All Subjects Treated

Trials: 003, 005, 006, 007, 008, 009, 013, 014, 019, 030, 035, 036, 037, 040, 041, 042, 043, 044, 045, 046, 048, 061, 063, 075, 077, 083, 084, 098, 099

Controlled Trials	Placebo (n=405)	Meloxicam 7.5 mg. (n=665)	Meloxicam 15 mg (n=1631)	Meloxicam 22.5 mg (n=338)	Meloxicam 30 mg (n=601)
Mean Exposure[1]	51 Days	75 Days	81 Days	116 Days	29Days
Median Exposure[1]	21 Days	23 Days	42 Days	84 Days	21 Days
Patients with GI Events	13.3%	20.2%	20.4%	32.2%	20.5%
Time till Onset of Initial GI Event- Cumulative probability of Experiencing a GI Event					
Day 7	6.6%	6.6%	5.9%	9.2%	8.4%
Day 21	12.2%	11.8%	11.8%	17.4%	15.3%
Day 84	20.0%	23.0%	22.8%	30.0%	37.9%
Day 168	23.7%	27.3%	26.7%	34.6%	45.8%
Patients at Risk on Day 168	38	187	405	71	4

On June 22, 1990 the sponsor decided to terminate use of the 30mg/d dose on the basis of an "unacceptably high incidence (crude rate of 3.2%) of severe gastrointestinal adverse events," including hematemasis, melana, and perforated gastric ulcers. In the eventual full database of controlled use of 30mg/d of meloxicam in OA and RA (n=1044), there was a 37.3%, 43.3%, and 19.3% incidence of mild, moderate, and severe GI events, respectively.

The sponsor did a pooled analysis of 15,071 patients treated with meloxicam 7.5 to 30mg in osteoarthrits, rheumatoid arthritis, or ankylosing spondylitis. This analysis showed an incidence of 0.03% at 7.5mg, 0.30% at 15mg, 0.66% at 22.5% and 0.96% at 30mg. If one looks at the six month incidence of serious upper GI complications by dose, the following are obtained: 0.16% for 7.5mg, 0.31% for 15mg, 0.5% for 22.5%, and 3.34% for 30mg.

Conclusion: A dose-toxicity effect is evident at higher doses (22.5 and 30mg).

TIME DEPENDENT ANALYSES: ALL GI EVENTS, PERFORATIONS/ULCERS/ BLEEDS

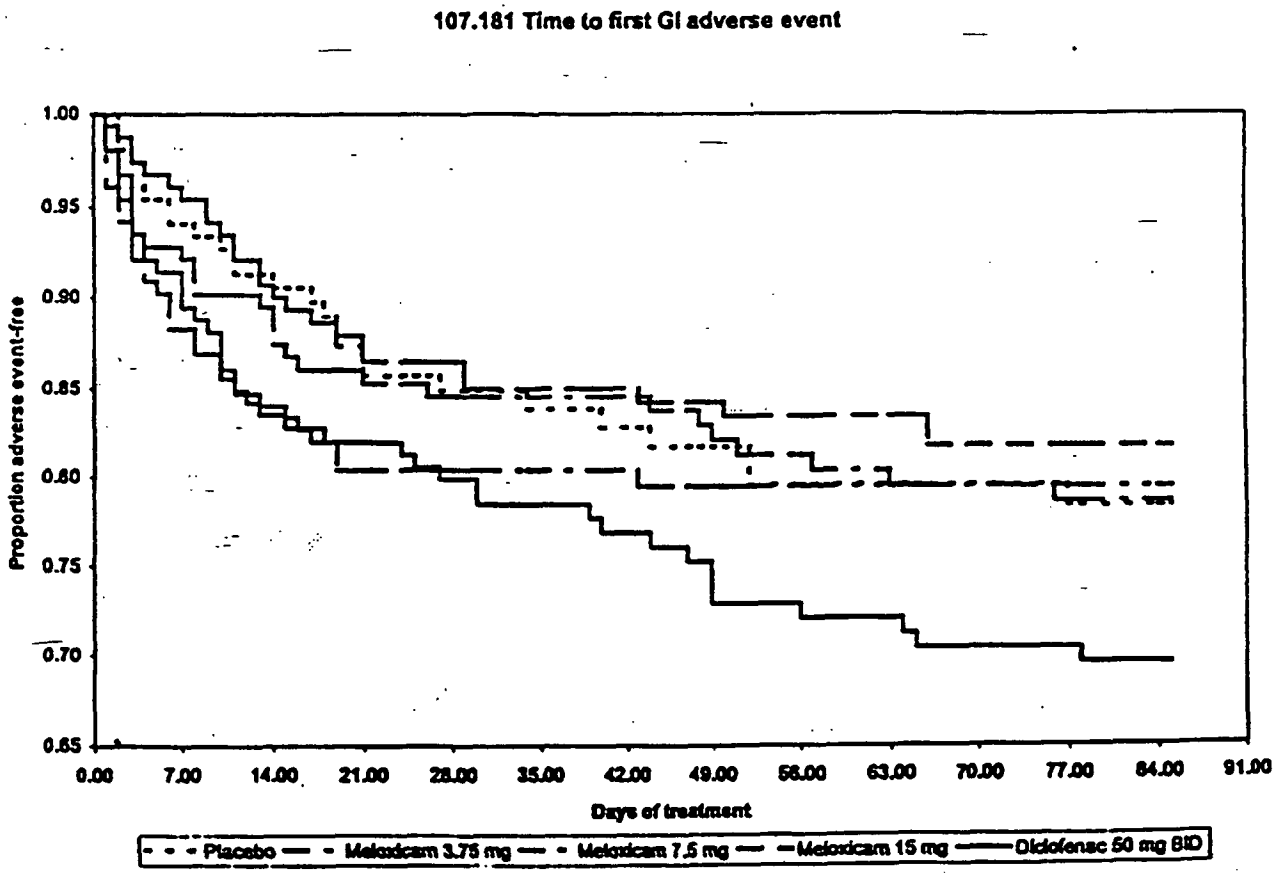
To compare, without bias, time-to-events by survival analysis requires combining only trials of the same design, whether placebo and active control, or active control alone.

A) Placebo-control trials. There was only one trial, #181, in which no PUBs were reported.

The crude rates for GI events were:

19.5%	3.75mg/d meloxicam (n=154)
20.1%	7.5mg/d meloxicam (n=154)
17.3%	15.0mg/d meloxicam (n=156)
28.1%	100mg/d diclofenac (n=153)
17.2%	placebo (n=157)

The cumulative probability graph is below. Only one pairwise comparison (2-tailed, logrank test) was statistically significant: meloxicam 15mg vs. diclofenac, p=0.019.



B) One month trials of OA of hip/knee/hands-spine: trials #153 and 154.

The crude rates for GI events were:

13.3%	7.5mg/d meloxicam	4635	(#153)
18.8%	100mg/d diclofenac	4688	
10.3%	7.5% mg/d meloxicam	4320	(#154)
15.3%	20mg/d piroxicam	4336	

The cumulative probability graph is shown below; both are statistically significant at a p=0.0001 level.

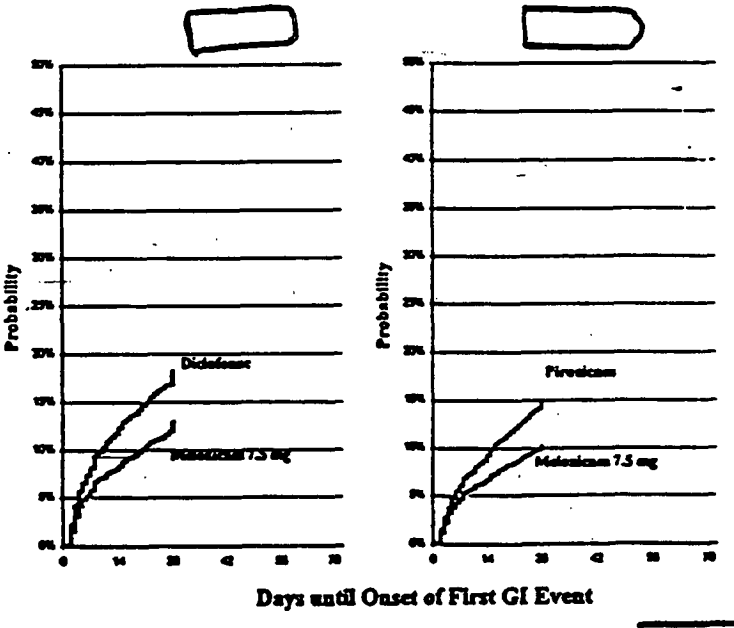
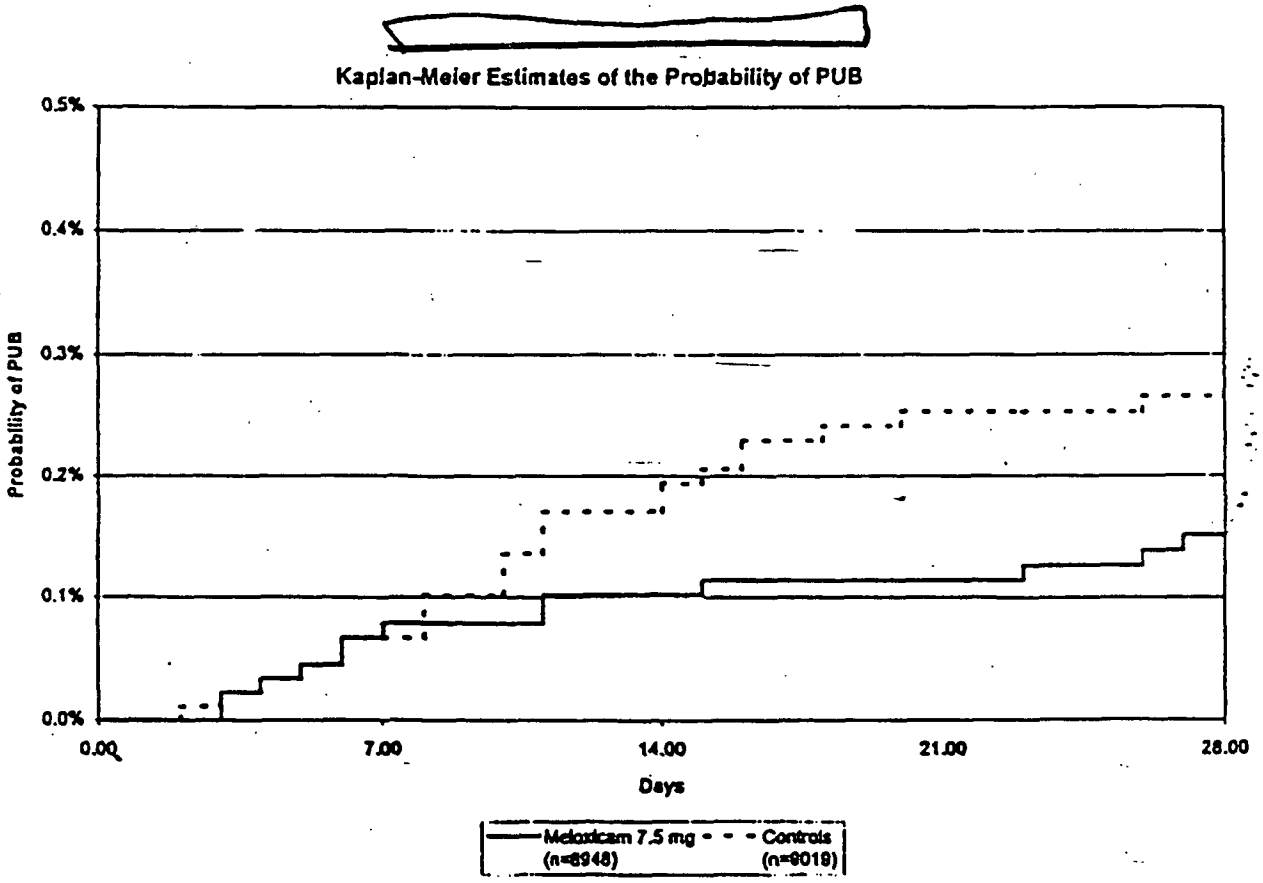


FIGURE 8.8.7.5.2: 2 Cumulative Probability of Developing a GI AE

The number of PUBs in these two trials was small. The Kaplan-Meier estimates othe probability of a PUB are shown below. The difference did not reach statistical significance (p=0.12).



Conclusion: Although GI AEes were not the prespecified hypothesis, this post hoc analysis did show statistical significance.

LABORATORY-ADVERSE EVENTS

Standard hematology and chemistry values were evaluated in an analysis of all diclofenac or piroxicam controlled trials, a database which was overwhelmingly patients in trials #153 and 154. Three analyses were done:

1) change from baseline mean and standard deviation
2) number of patients shifting from normal to high, or normal to low
3) number of patients showing a "clinically significant" value - defined as follows:

Hb	<11.5-male, <9.5-female
Hct	<37%-male, <32-female
WBC	<2800, >16000
neutr.	<15%. >90%
plt.	<75K, >700K
Na	<115, >155
K	<3.0, >5.8
gluc.	<50, >180
ALT	>3xULN
AST	>3xULN
alk phos	>3xULN
creat	>2.0

TABLE 8.8.8.1: 2 Hematology Summary for Diclofenac and Piroxicam Active-Controlled Phase 2/3 Trials (Integrated Safety Database)

Analyte		Meloxicam (all doses) (N=9573)	Piroxicam (N=4537)	Diclofenac SR (N=4551)
Hemoglobin (g/dL)				
Change from baseline to last visit[1]				
N		9327	4409	4466
Mean		-0.07	-0.22	-0.17
SD		0.78	0.83	0.73
Notable shifts[2]	N	9327	4409	4466
Downward[3]	n (%)	420 4.5%	250 5.7%	222 5.0%
Upward[4]	n (%)	143 1.5%	56 1.3%	66 1.5%
Clinically significant[5]	N	7747	3648	3825
Low	n (%)	54 0.7%	24 <0.7%	7 0.2
Hematocrit (%)				
Change from baseline to last visit[1]				
N		9320	4400	4459
Mean		0.1	-0.3	-0.1
SD		2.9	3.0	2.8
Notable shifts[2]	N	9319	4400	4459
Downward[3]	n (%)	463 5.0%	282 6.4%	195 4.4%
Upward[4]	n (%)	237 2.5%	88 2.0%	93 2.1%
Clinically significant[5]	N	8178	3849	3959
Low	n (%)	81 1.0%	52 1.4%	20 0.5%
RBC ($x10^{6}/mm^{3}$)				
Change from baseline to last visit[1]				
N		9292	4389	4447
Mean		-0.01	-0.06	-0.05
SD		0.28	0.29	0.26
Notable shifts[2]	N	9292	4389	4447
Downward[3]	n (%)	481 5.2%	321 7.3%	216 4.9%
Upward[4]	n (%)	91 1.0%	29 0.7%	28 0.6%
Clinically significant[5]	N	8104	3836	3911
Low	n (%)	13 0.2%	10 0.3%	7 0.2%

1 A patient must have had a baseline and at least one postbaseline laboratory result to be included in this number.

2 "N" is the number of patients who had baseline and post-baseline results, and "n" is the number of patients with notable downward/upward shifts. Percentages are based on "N."

3 A notable downward shift is any shift from normal, high, or clinically significantly high at baseline to low or clinically significantly low at any time postbaseline.

4 A notable upward shift is any shift from normal, low, or clinically significantly low at baseline to high or clinically significantly high at any time postbaseline.

5 "N" is the number of patients with data for the laboratory test during treatment, and "n" is the

Analyte		Meloxicam (all doses) (N=9573)	Piroxicam (N=4537)	Diclofenac SR (N=4551)
WBC ($\times 10^3/mm^3$)				
Change from baseline to last visit[1]				
N		9313	4404	4453
Mean		-0.12	0.03	-0.10
SD		1.55	1.62	1.61
Notable shifts[2]	N	9313	4404	4453
Downward[3]	n (%)	346 3.7%	144 3.3%	139 3.1%
Upward[4]	n (%)	263 2.8%	169 3.8%	98 2.2%
Clinically significant[5]	N	8374	3895	4086
High	n (%)	7 <0.1%	1 <0.1%	5 0.1%
Low	n (%)	10 0.1%	1 <0.1%	3 <0.1%
Lymphocytes (%)				
Change from baseline to last visit[1]				
N		6332	2967	3047
Mean		0.4	-0.6	0.2
SD		7.4	7.1	7.6
Notable shifts[2]	N	8971	4208	4438
Downward[3]	n (%)	481 5.4%	241 5.7%	209 4.7%
Upward[4]	n (%)	265 3.0%	48 1.1%	175 3.9%
Clinically significant[5]	N	7702	3615	3795
Low	n (%)	22 0.3%	11 0.3%	8 0.2%
Neutrophils (%)				
Change from baseline to last visit[1]				
N		6332	2968	3047
Mean		-0.5	0.3	0.2
SD		8.4	7.9	7.6
Notable shifts[2]	N	8971	4208	4437
Downward[3]	n (%)	385 4.3%	84 2.0%	272 6.1%
Upward[4]	n (%)	347 3.9%	173 4.1%	139 3.1%
Clinically significant[5]	N	7696	3772	3658
High	n (%)	1 <0.1%	0 0.0	3 <0.1%
Low	n (%)	1 <0.1%	0 0.0	0 0.0
Eosinophils (%)				
Change from baseline to last visit[1]				
N		6252	2936	2995
Mean		0.0	0.2	0.2
SD		1.7	2.5	1.9
Notable shifts[2]	N	8872	4173	4375
Downward[3]	n (%)	118 1.3%	42 1.0%	42 1.0%
Upward[4]	n (%)	312 3.5%	140 3.4%	248 5.7%
Clinically significant[5]	N	8008	3841	3887
High	n (%)	24 0.3%	9 0.2	15 0.4
Basophils (%)				
Change from baseline to last visit[1]				
N		6095	2897	2909
Mean		0.0	0.0	0.1
SD		0.7	0.5	0.6
Notable shifts[2]	N	8668	4088	4267
Downward[3]	n (%)	16 0.2%	5 0.1%	8 0.2%
Upward[4]	n (%)	255 2.9%	128 3.1%	90 2.1%
Clinically significant[5]	N	8259	3878	4140
High	n (%)	8 <0.1%	4 0.1%	3 <0.1%
Monocytes				
Change from baseline to last visit[1]				
N		6280	2943	3020
Mean		0.1	0.0	0.2
SD		2.3	2.1	2.3
Notable shifts[2]	N	8912	4178	4402
Downward[3]	n (%)	212 2.4%	93 2.2%	90 2.0%
Upward[4]	n (%)	395 4.4%	128 3.1%	180 4.1%
Clinically significant[5]	N	8045	3834	3985
High	n (%)	4 <0.1%	1 <0.1%	1 <0.1%
Thrombocytes				
Change from baseline to last visit[1]				
N		9298	4391	4448
Mean		-3.7	1.5	-0.2
SD		40.5	41.4	38.9
Notable shifts[2]	N	9298	4391	4448
Downward[3]	n (%)	135 1.5%	61 1.4%	72 1.6%
Upward[4]	n (%)	161 1.8%	94 2.1%	50 1.1%
Clinically significant[5]	N	8709	4150	4214
High	n (%)	0 0.0	1 <0.1%	0 0.0
Low	n (%)	5 <0.1%	3 <0.1%	2 <0.1%

Analyte		Meloxicam (all doses) (N=9573)	Piroxicam (N=4551)	Diclofenac SR (N=4537)
SGOT (U/L)				
Change from baseline to last visit[1]				
N		9528	4512	4528
Mean		-0.1	-0.3	1.7
SD		8.0	6.7	11.0
Notable shifts[2]	N	9528	4512	4528
Downward[3]	n (%)	35 0.4%	10 0.2%	10 0.2%
Upward[4]	n (%)	293 3.1%	102 2.3%	251 5.5%
Clinically significant[5]	N	9031	4256	4297
High	n (%)	8 <0.1%	2 <0.1%	9 0.2%
SGPT (U/L)				
Change from baseline to last visit[1]				
N		9523	4511	4524
Mean		-0.3	0.0	4.5
SD		11.2	9.2	17.6
Notable shifts[2]	N	9523	4511	4524
Downward[3]	n (%)	65 0.7%	26 0.6%	3 <0.1%
Upward[4]	n (%)	371 3.9%	197 4.4%	453 10.0%
Clinically significant[5]	N	8627	4091	4101
High	n (%)	15 0.2%	7 0.2%	26 0.6%
(U/L)				
Change from baseline to last visit[1]				
N		9516	4493	4519
Mean		-2.3	0.2	0.5
SD		23.0	24.2	21.8
Notable shifts[2]	N	9516	4493	4520
Downward[3]	n (%)	76 0.8%	35 0.8%	35 0.8%
Upward[4]	n (%)	170 1.8%	104 2.3%	95 2.1%
Clinically significant[5]	N	8678	4096	4181
High	n (%)	1 <0.1%	0 0.0	1 <0.1%
GGT (U/L)				
Change from baseline to last visit[1]				
N		1292	608	319
Mean		3.4	0.5	6.9
SD		33.1	18.0	34.3
Notable shifts[2]	N	1292	608	319
Downward[3]	n (%)	11 0.9%	3 0.5%	1 0.3%
Upward[4]	n (%)	105 8.1%	49 8.1%	35 11.0%
Clinically significant[5]	N	1091	501	271
High	n (%)	9 0.8%	2 0.4	1 0.4%

Analyte		Meloxicam (all doses) (9573)	Piroxicam (4537)	Diclofenac SR (4551)
Creatinine (mg/dL)				
Change from baseline to last visit[1]				
N		9530	4508	4522
Mean		0.01	0.02	0.01
SD		0.14	0.15	0.17
Notable shifts[2]	N	9530	4508	4522
Downward[3]	n (%)	82 0.9%	35 0.8%	29 0.6%
Upward[4]	n (%)	259 2.7%	173 3.8%	166 3.7%
Clinically significant[5]	N	8838	4178	4242
High	n (%)	10 <0.1%	2 <0.1%	3 <0.1%
Sodium (mEq/L)				
Change from baseline to last visit[1]				
N		1295	607	318
Mean		-0.2	-0.1	-0.4
SD		3.3	3.2	3.4
Notable shifts[2]	N	1295	607	318
Downward[3]	n (%)	83 6.4%	39 6.4%	14 4.4%
Upward[4]	n (%)	54 4.2%	31 5.1%	7 2.2%
Clinically significant[5]	N	1229	572	297
High	n (%)	3 0.2%	3 0.5%	0 0.0%
Potassium (mEq/L)				
Change from baseline to last visit[1]				
N		1288	607	314
Mean		0.02	0.05	0.04
SD		0.52	0.50	0.67
Notable shifts[2]	N	1288	607	314
Downward[3]	n (%)	38 3.0%	11 1.8%	12 3.8%
Upward[4]	n (%)	100 7.8%	47 7.7%	18 5.7%
Clinically significant[5]	N	1217	577	299
High	n (%)	36 3.0%	22 3.8%	3 1.0%
Glucose (mg/dL)				
Change from baseline to last visit[1]				
N		761	248	317
Mean		0.38	2.10	-4.87
SD		29.53	33.48	40.31
Notable shifts[2]	N	761	248	317
Downward[3]	n (%)	15 2.0%	2 0.8%	5 1.6%
Upward[4]	n (%)	123 16.2%	64 25.8%	65 14.8%
Clinically significant[5]	N	598	205	242
High	n (%)	6 1.0%	3 1.5%	1 0.4
Low	n (%)	7 1.2%	2 1.0%	2 0.8

Discussion: The above table omits bilirubin. The results of trial #181 are reassuring in this regard, showing no patients in any arm with a bilirubin increase to 2 or more. I can find no record of bicarbonate or chloride results although no cases of clinical renal tubular acidosis were reported. I have asked the sponsor for these data, if they exist.

TOXICITY PROFILE IN SUBSETS

AGE / GENDER: A 14 day PK study (#085) of 28 RA patients, ages 31-80, 13 male / 15 female, found similar meloxicam kinetics between young and elderly males, but elderly females had a larger AUC (by 21%) and Cmax (by 15%) per 10 years age, compared to younger females. Other population-kinetic studies confirmed that elderly females showed higher concentrations and decreased clearances. The two tables below, showing organ-based AEs by age and by gender, do not reveal any meaningful differeneces. Clinical and laboratory AEs (using the same conventions as above) for patients subdivided by both age and gender (men <65, women <65, men 65-75, women 65-75, men >75, and women >75) are shown in appendices 9 and 10. No notable differences are seen.

TABLE 8.8.12.2: 1 Incidence of Treatment-Emergent AEs by System-Organ Class and Age for Diclofenac and Piroxicam Active-Controlled Phase 2/3 Trials (Integrated Safety Database)

System-Organ Class	Age (years)								
	<=65 years			66-75 years			> 75 years		
	Meloxicam (n=7698) n %	Diclofenac (n=3212) n %	Piroxicam (n=3615) n %	Meloxicam (n=3064) n %	Diclofenac (n=1506) n %	Piroxicam (n=1412) n %	Meloxicam (n=1317) n %	Diclofenac (n=701) n %	Piroxicam (n=602) n %
Total With Any AE	2246 29.2	980 30.5	1134 31.4	853 27.8	515 34.2	457 32.4	372 28.2	251 35.8	188 31.2
Application Site Disorders	6 <0.1	0	0	1 <0.1	0	0	0	0	0
Body As A Whole - General Disorders	363 4.7	121 3.8	186 5.1	126 4.1	64 4.2	76 5.4	59 4.5	26 3.7	36 6.0
Cardiovascular Disorders, General	52 0.7	11 0.3	24 0.7	24 0.8	11 0.7	27 1.9	16 1.2	5 0.7	6 1.0
Centr & Periph Nervous System Disorders	404 5.2	133 4.1	157 4.3	132 4.3	81 5.4	63 4.5	63 4.8	39 5.6	21 3.5
Collagen Disorders	2 <0.1	0	0	0	1 <0.1	0	0	0	0
Endocrine Disorders	3 <0.1	1 <0.1	2 <0.1	2 <0.1	0	0	0	0	0
Foetal Disorders[1]	0	0	1 <0.1	0	0	0	0	0	0
Gastro-Intestinal System Disorders	1090 14.2	577 18.0	637 17.6	401 13.1	298 19.8	235 16.6	154 11.7	139 19.8	89 14.8
Hearing And Vestibular Disorders	18 0.2	7 0.2	9 0.2	9 0.3	2 0.1	4 0.3	2 0.2	2 0.3	1 0.2
Heart Rate And Rhythm Disorders	24 0.3	14 0.4	13 0.4	17 0.6	4 0.3	4 0.3	8 0.6	4 0.6	2 0.3
Liver And Biliary System Disorders	28 0.4	22 0.7	15 0.4	8 0.3	10 0.7	6 0.4	4 0.3	4 0.6	2 0.3
Metabolic And Nutritional Disorders	26 0.3	10 0.3	11 0.3	11 0.4	3 0.2	6 0.4	8 0.6	1 0.1	2 0.3
Musculo-Skeletal System Disorders	260 3.4	73 2.3	115 3.2	78 2.5	30 2.0	26 1.8	26 2.0	16 2.3	13 2.2
Myo Endo Pericardial & Valve Disorders	9 0.1	2 <0.1	6 0.2	10 0.3	5 0.3	4 0.3	5 0.4	3 0.4	1 0.2
Neoplasm	12 0.2	2 <0.1	5 0.1	5 0.2	3 0.2	3 0.2	0	2 0.3	1 0.2
Platelet,Bleeding & Clotting Disorders	33 0.4	13 0.4	17 0.5	10 0.3	4 0.3	7 0.5	7 0.5	3 0.4	2 0.3
Psychiatric Disorders	146 1.9	45 1.4	75 2.1	41 1.3	31 2.1	16 1.1	19 1.4	8 1.1	4 0.7
Red Blood Cell Disorders	20 0.3	5 0.2	15 0.4	15 0.5	8 0.5	5 0.4	7 0.5	4 0.6	4 0.7
Reproductive Disorders, Female	27 0.4	7 0.2	9 0.2	2 <0.1	2 0.1	1 <0.1	2 0.2	1 0.1	0
Reproductive Disorders, Male	7 <0.1	1 <0.1	5 0.1	4 0.1	0	1 <0.1	2 0.2	1 0.1	0
Resistance Mechanism Disorders	65 0.8	18 0.6	41 1.1	13 0.4	8 0.5	9 0.6	3 0.2	0	3 0.5
Respiratory System Disorders	270 3.5	106 3.3	103 2.8	99 3.2	51 3.4	39 2.8	28 2.1	24 3.4	20 3.3
Skin And Appendages Disorders	237 3.1	69 2.1	97 2.7	68 2.2	25 1.7	31 2.2	28 2.1	14 2.0	9 1.5
Special Senses Other, Disorders	8 0.1	5 0.2	8 0.2	4 0.1	3 0.2	2 0.1	1 <0.1	0	0
Urinary System Disorders	119 1.5	33 1.0	61 1.7	67 2.2	35 2.3	47 3.3	43 3.3	27 3.9	18 3.0
Vascular (Extracardiac) Disorders	16 0.2	9 0.3	10 0.3	20 0.7	7 0.5	5 0.4	8 0.6	9 1.3	1 0.2
Vision Disorders	69 0.9	12 0.4	24 0.7	22 0.7	8 0.5	12 0.8	7 0.5	3 0.4	7 1.2
White Cell And RES Disorders	23 0.3	5 0.2	7 0.2	8 0.3	5 0.3	4 0.3	2 0.2	1 0.1	2 0.3

1 The patient (107.154/72502/68956; 41-year-old female) was reported to have had a congenital hernia which according to the WHO Dictionary is coded in the Foetal Disorders Category.
Source: TABLE P.1.2

TABLE 8.8.12.3: 1 Incidence of Treatment-Emergent AEs by System-Organ Class and Gender for Diclofenac and Piroxicam Active-Controlled Phase 2/3 Trials (Integrated Safety Database)

System-Organ Class	Gender					
	Male			Female		
	Meloxicam (n=4113) n %	Diclofenac (n=1829) n %	Piroxicam (n=1900) n %	Meloxicam (n=7972) n %	Diclofenac (n=3596) n %	Piroxicam (n=3731) n %
TOTAL WITH ANY AE	1138 27.7	563 30.8	560 29.5	2334 29.3	1184 32.9	1219 32.7
Application Site Disorders	1 <0.1	0	0	6 <0.1	0	0
Autonomic Nervous System Disorders	0	0	0	0	0	0
Body As A Whole - General Disorders	170 4.1	57 3.1	92 4.8	378 4.7	154 4.3	206 5.5
Cardiovascular Disorders, General	20 0.5	16 0.9	14 0.7	72 0.9	12 0.3	43 1.2
Cent & Periph Nervous System Disorders	175 4.3	84 4.6	65 3.4	425 5.3	169 4.7	176 4.7
Collagen Disorders	0	0	0	2 <0.1	1 <0.1	0
Endocrine Disorders	2 <0.1	0	1 <0.1	3 <0.1	1 <0.1	1 <0.1
Foetal Disorders[1]	0	0	0	0	0	1 <0.1
Gastro-Intestinal System Disorders	533 13.0	310 16.9	294 15.5	1113 14.0	704 19.6	667 17.9
Hearing And Vestibular Disorders	10 0.2	2 0.1	5 0.3	19 0.2	9 0.3	9 0.2
Heart Rate And Rhythm Disorders	10 0.2	9 0.5	1 <0.1	39 0.5	13 0.4	18 0.5
Liver And Biliary System Disorders	12 0.3	9 0.5	5 0.3	28 0.4	27 0.8	18 0.5
Metabolic And Nutritional Disorders	14 0.3	4 0.2	12 0.6	31 0.4	10 0.3	7 0.2
Musculo-Skeletal System Disorders	139 3.4	47 2.6	65 3.4	225 2.8	72 2.0	89 2.4
Myo Endo Pericardial & Valve Disorders	12 0.3	5 0.3	4 0.2	12 0.2	5 0.1	7 0.2
Neoplasm	5 0.1	1 <0.1	2 0.1	12 0.2	6 0.2	7 0.2
Platelet, Bleeding & Clotting Disorders	17 0.4	7 0.4	6 0.3	33 0.4	13 0.4	20 0.5
Psychiatric Disorders	67 1.6	27 1.5	37 1.9	139 1.7	57 1.6	58 1.6
Red Blood Cell Disorders	7 0.2	5 0.3	9 0.5	35 0.4	12 0.3	15 0.4
Reproductive Disorders, Female	0	0	0	31 0.4	10 0.3	10 0.3
Reproductive Disorders, Male	12 0.3	2 0.1	6 0.3	1 <0.1	0	0
Resistance Mechanism Disorders	32 0.8	9 0.5	17 0.9	49 0.6	17 0.5	36 1.0
Respiratory System Disorders	146 3.5	71 3.9	47 2.5	251 3.1	110 3.1	115 3.1
Secondary Terms	0	0	0	0	0	0
Skin And Appendages Disorders	101 2.5	39 2.1	50 2.6	231 2.9	69 1.9	87 2.3
Special Senses Other, Disorders	2 <0.1	4 0.2	4 0.2	11 0.1	4 0.1	6 0.2
Urinary System Disorders	68 1.7	32 1.7	35 1.8	161 2.0	63 1.8	91 2.4
Vascular (Extracardiac) Disorders	11 0.3	11 0.6	8 0.4	33 0.4	14 0.4	8 0.2
Vision Disorders	43 1.0	6 0.3	19 1.0	55 0.7	17 0.5	24 0.6
White Cell And RES Disorders	7 0.2	4 0.2	1 <0.1	26 0.3	7 0.2	12 0.3

1 The patient (107.154/72502/68956; 41-year-old female) was reported to have had a congenital hernia which according to the WHO Dictionary is coded in the Foetal Disorders Category. Source: TABLE P.2.2

RACE: Although databases are small – blacks:122, other non-Caucasians:63 – there are no obvious differences in the safety profile across races.

TABLE 8.8.12.5: 1 Incidence of Treatment-Emergent AEs by System-Organ Class and Race for Diclofenac and Piroxicam Active-Controlled Phase 2/3 Trials (Integrated Safety Database)

	Caucasian			Black			Other		
System-Organ Class	Meloxicam (All Doses) (n=9967) n %	Diclofenac (n=3906) n %	Piroxicam (n=5265) n %	Meloxicam (All Doses) (n=122) n %	Diclofenac (n=49) n %	Piroxicam (n=62) n %	Meloxicam (All Doses) (n=63) n %	Diclofenac (n=20) n %	Piroxicam (n=29) n %
TOTAL WITH ANY AE	2934 29.4	1360 34.8	1649 31.3	37 30.3	21 42.9	23 37.1	29 46.0	12 60.0	11 37.9
Application Site Disorders	4 <0.1	0	0	0	0	0	0	0	0
Autonomic Nervous System Disorders	0	0	0	0	0	0	0	0	0
Body As A Whole - General Disorders	473 4.7	167 4.3	286 5.4	6 4.9	3 6.1	5 8.1	6 9.5	0	2 6.9
Cardiovascular Disorders, General	76 0.8	27 0.7	53 1.0	1 0.8	0	0	0	0	0
Centr & Periph Nervous System Disorders	517 5.2	208 5.3	224 4.3	6 4.9	5 10.2	3 4.8	3 4.8	2 10.0	3 10.3
Collagen Disorders	2 <0.1	1 <0.1	0	0	0	0	0	0	0
Endocrine Disorders	5 <0.1	1 <0.1	2 <0.1	0	0	0	0	0	0
Foetal Disorders[1]	0	0	1 <0.1	0	0	0	0	0	0
Gastro-Intestinal System Disorders	1378 13.8	779 19.9	892 16.9	18 14.8	9 18.4	12 19.4	14 22.3	6 30.0	5 17.2
Hearing And Vestibular Disorders	25 0.3	8 0.2	13 0.2	0	1 2.0	1 1.6	0	0	0
Heart Rate And Rhythm Disorders	43 0.4	17 0.4	17 0.3	1 0.8	1 2.0	0	0	0	0
Liver And Biliary Syste.n Disorders	34 0.3	32 0.8	23 0.4	0	0	0	0	0	0
Metabolic And Nutritional Disorders	37 0.4	9 0.2	17 0.3	0	1 2.0	2 3.2	1 1.6	1 5.0	0
Musculo-Skeletal System Disorders	326 3.3	101 2.6	141 2.7	6 4.9	1 2.0	0	1 1.6	0	1 3.4
Myo Endo Pericardial & Valve Disorders	20 0.2	9 0.2	8 0.2	0	0	0	0	0	0
Neoplasm	12 0.1	4 0.1	9 0.2	1 0.8	0	0	1 1.6	0	0
Platelet, Bleeding & Clotting Disorders	43 0.4	12 0.3	25 0.5	3 2.5	1 2.0	0	0	0	0
Psychiatric Disorders	165 1.7	69 1.8	92 1.7	1 0.8	1 2.0	-	2 3.2	1 5.0	-
Red Blood Cell Disorders	38 0.4	12 0.3	22 0.4	1 0.8	0	0	1 1.6	2 10.0	1 3.4
Reproductive Disorders, Female	24 0.2	9 0.2	9 0.2	1 0.8	0	1 1.6	0	0	0
Reproductive Disorders, Male	10 <0.1	2 <0.1	5 <0.1	0	0	0	0	0	0
Resistance Mechanism Disorders	76 0.8	22 0.6	48 0.9	0	0	0	0	1 5.0	0
Respiratory System Disorders	354 3.6	138 3.5	151 2.9	2 1.6	4 8.2	2 3.2	4 6.3	2 10.0	2 6.9
Skin And Appendages Disorders	267 2.7	86 2.2	125 2.4	6 4.9	3 6.1	1 1.6	6 9.5	1 5.0	1 3.4
Special Senses Other, Disorders	12 0.1	6 0.2	10 0.2	0	1 2.0	0	0	0	0
Urinary System Disorders	206 2.1	79 2.0	116 2.2	3 2.5	1 2.0	3 4.8	1 1.6	1 5.0	0
Vascular (Extracardiac) Disorders	38 0.4	18 0.5	14 0.3	1 0.8	0	0	0	0	0
Vision Disorders	90 0.9	22 0.6	37 0.7	0	1 2.0	1 1.6	1 1.6	0	0
White Cell And RES Disorders	28 0.3	9 0.2	12 0.2	0	1 2.0	0	0	0	0

1 The patient (107.154/72502/68936;41-year-old female) was reported to have had a congenital hernia which according to the WHO Dictionary is coded in the Foetal Disorders Category.
Source: TABLE P.4.2

DISEASE: In a 9 day study in renal-impaired patients, no further deterioration occurred on 15mg meloxicam, and a similar was obtained in a 28 day study of 25 patients with rheumatic disease and renal impariment. Plasma levels decreased as ranl impairment increased, but the plasma free fraction was higher than that found in normal volunteers, presumably accounting for the increased total clearance seen. These findings do not support a dose adjustment of meloxicam in patients with renal insufficiency. Nonetheless, the dose recommended is 7.5mg/d.

Only a single dose PK study was done in 16 patients with hepatic insufficiency (clinically stable liver sirrhosis and moderately imparied hepatic function), where lower concentrations, lower AUCs, and higher clearances were found, so a dose adjustment is not deemed necessary.

DRUG-DRUG INTERACTION

INTERACTION STUDIES: A variety of drug-drug interaction studies were conducted. They are listed in appendix 11. One drug, lithium, showed an increase in blood levels by 21%, a known effect of many NSAIDs via the inhibition of prostaglandin synthetase. A mild increase in methotrexate concentrations (9%) was also seen. This will need to be looked at critically if meloxicam is submitted for RA, and may deserve label mention even now as a precaution. An increased meloxicam clearance was seen with cholestyramine, with possible application to overdose or severe drug toxicity.

ADVERSE EVENT ANALYSES: Tables of events are given for three concomitant medications: salicylates, ace-inhibitors/beta-blockers/diuretics, and anti-coagulants.

TABLE 8.8.10.2: 2 Incidence of Treatment-Emergent AEs by WHOART Preferred Term and Salicylate Use in Diclofenac and Piroxicam Active-Controlled Phase 2/3 Trials (Integrated Safety Database)

	Patients Who Took Salicylates			Patients Who Did Not Take Salicylates		
WHOART Preferred Term	Meloxicam (All Doses) (N=92)	Diclofenac SR (N=30)	Piroxicam (N=46)	Meloxicam (All Doses) (N=11795)	Diclofenac SR (N=5304)	Piroxicam (N=5575)
	n %	n %	n %	n %	n %	n %
Total w/Any NSAID-Associated AE	16 17.4	9 30.0	8 17.4	1238 10.5	768 14.5	750 13.5
Nausea	6 6.5	2 6.7	0	332 2.8	171 3.2	183 3.3
Dyspepsia	5 5.4	2 6.7	7 15.2	558 4.7	318 6.0	344 6.2
Abdominal Pain	4 4.3	4 13.3	0	341 2.9	290 5.5	224 4.0
Vomiting	2 2.2	0	1 2.2	90 0.8	48 0.9	48 0.9
Gastric Ulcer	1 1.1	1 3.3	0	4 <0.1	2 <0.1	7 0.1
Duodenal Ulcer	1 1.1	0	0	2 <0.1	0	9 0.2
Haematemesis	1 1.1	0	0	2 <0.1	0	0
Gastritis	0	3 10.0	1 2.2	51 0.4	32 0.6	33 0.6
Gastroenteritis	0	1 3.3	1 2.2	20 0.2	18 0.3	17 0.3
Gastro-Intestinal Disorder NOS	0	0	0	18 0.2	5 <0.1	8 0.1
Anorexia	0	0	0	17 0.1	10 0.2	6 0.1
GI Haemorrhage	0	0	0	15 0.1	2 <0.1	6 0.1
Melaena	0	0	0	9 <0.1	3 <0.1	9 0.2
Gastroesophageal Reflux	0	0	0	5 <0.1	3 <0.1	0
Duodenal Ulcer Perforated	0	0	0	2 <0.1	2 <0.1	0
Gastric Ulcer Haemorrhagic	0	0	0	1 <0.1	1 <0.1	2 <0.1
Duodenal Ulcer Haemorrhagic	0	0	0	0	1 <0.1	1 <0.1
Duodenal Ulcer Reactivated	0	0	0	0	0	1 <0.1
Gastric Ulcer Perforated	0	0	0	0	0	3 <0.1
Gastritis Haemorrhagic	0	0	0	0	0	1 <0.1

Source: TABLE N.2.2

TABLE 8.8.10.2: 4 Incidence of Treatment-Emergent AEs by WHOART Preferred Term and ACE Inhibitor, Beta Blocker, or Diuretic Use in Diclofenac and Piroxicam Active-Controlled Phase 2/3 Trials (Integrated Safety Database)

	Patients Who Took ACE Inhibitors, Beta-Blockers, or Diuretics			Patients Who Did Not Take ACE Inhibitors, Beta-Blockers, or Diuretics		
WHOART Preferred Term	Meloxicam (All Doses) (N=232)	Diclofenac (N=83)	Piroxicam (N=145)	Meloxicam (All Doses) (N=11655)	Diclofenac (N=5251)	Piroxicam (N=5476)
	n %	n %	n %	n %	n %	n %
Total w/Any NSAID-Associated AE	54 23.3	19 22.9	43 29.7	155 1.3	87 1.7	127 2.3
Hypertension	25 10.8	4 4.8	14 9.7	26 0.2	14 0.3	16 0.3
Oedema Peripheral	14 6.0	8 9.6	16 11.0	41 0.4	25 0.5	31 0.6
Hypertension Aggravated	9 3.9	1 1.2	6 4.1	6 <0.1	1 <0.1	8 0.1
Oedema Generalised	4 1.7	1 1.2	0	6 <0.1	0	5 <0.1
Cardiac Failure	4 1.7	4 4.8	2 1.4	4 <0.1	1 <0.1	0
Oedema Dependent	3 1.3	1 1.2	4 2.8	11 <0.1	3 <0.1	18 0.3
Renal Function Abnormal	2 0.9	0	1 0.7	4 <0.1	5 <0.1	4 <0.1
Oedema	1 0.4	1 1.2	2 1.4	19 0.2	5 <0.1	9 0.2
BUN Increased	0	1 1.2	3 2.1	35 0.3	26 0.5	30 0.5
NPN Increased	0	1 1.2	0	13 0.1	15 0.3	12 0.2
Circulatory Failure	0	0	1 0.7	4 <0.1	1 <0.1	2 <0.1
Oliguria	0	0	0	1 <0.1	1 <0.1	2 <0.1
Renal Failure Acute	0	0	0	1 <0.1	1 <0.1	0
Cardiac Failure Left	0	0	0	0	1 <0.1	0

Source: TABLE N.4.2

TABLE 8.8.10.2: 3 Incidence of Treatment-Emergent AEs by WHOART Preferred Term and Anticoagulant Use in Diclofenac and Piroxicam Active-Controlled Phase 2/3 Trials (Integrated Safety Database)

	Patients Who Took Anticoagulants			Patients Who Did Not Take Anticoagulants		
WHOART Preferred Term	Meloxicam (All Doses) (N=33)	Diclofenac (N=13)	Piroxicam (N=7)	Meloxicam (All Doses) (N=11856)	Diclofenac (N=5321)	Piroxicam (N=5614)
	n %	n %	n %	n %	n %	n %
Total w/Any NSAID-Associated AE	3 9.1	0	0	79 0.7	33 0.6	49 0.9
Purpura	2 6.1	0	0	10 <0.1	6 0.1	12 0.2
Haematemesis	1 3.0	0	0	2 <0.1	0	0
Epistaxis	0	0	0	21 0.2	7 0.1	6 0.1
GI Haemorrhage	0	0	0	15 0.1	2 <0.1	6 0.1
Haematuria	0	0	0	9 <0.1	2 <0.1	3 <0.1
Melaena	0	0	0	9 <0.1	3 <0.1	9 0.2
Haemorrhage Rectum	0	0	0	8 <0.1	9 0.2	6 0.1
Cerebral Haemorrhage	0	0	0	2 <0.1	0	0
Haematoma	0	0	0	2 <0.1	2 <0.1	4 <0.1
Haemorrhage NOS	0	0	0	2 <0.1	0	0
Gastric Ulcer Haemorrhagic	0	0	0	1 <0.1	1 <0.1	2 <0.1
Gingival Bleeding	0	0	0	1 <0.1	0	0
Diarrhoea Bloody	0	0	0	0	2 <0.1	0
Duodenal Ulcer	0	0	0	0	0	1 <0.1
Duodenal Ulcer Haemorrhagic	0	0	0	0	1 <0.1	1 <0.1
Gastritis Haemorrhagic	0	0	0	0	0	1 <0.1
Prothrombin Decreased	0	0	0	0	0	1 <0.1

Source: TABLE N.3.2

LONG-TERM EXPOSURE

Open exposure in OA on meloxicam 15mg/d was studied in trial #047, consisting of three populations, the first two treated for up to 24 months, the third for up to 18 months.

1. 282 patients begun de novo on meloxicam 15mg/d,
2. 143 patients: a subset of the 223 meloxicam 15mg/d completers of trial #045, and
3. 65 patients: a subset of the 98 piroxicam 20mg/d completers of trial #045,

These are called, respectively, Group I/direct, Group I/indirect, and Group II in the tables below. AE rates would be expected to be likely higher in the first group. The AE rates by category and by organ system are given below:

TABLE 8.8.14.1.2: 1 Overall Incidence of AEs in Long-Term Trial 107.047

Category	Group I[2]						Group II[3]		Total Safety Population	
	Direct-Entry[1]		Indirect-Entry		Total					
	n	%	n	%	n	%	n	%	n	%
Number of patients entered	282		143		425		65		490	
Patients without AEs	58	20.6	31	21.7	89	20.9	17	26.2	106	21.6
Patients with one or more AEs	224	79.4	112	78.3	336	79.1	48	73.8	384	78.4
Withdrawals due to AEs	73	25.9	17	11.9	90	21.1	7	10.8	97	19.8
Patients with SAEs	0	0	0	0	41	8.4	2	0.4	43	8.8
Deaths	2	0.7	2	0.7	4	0.9	0	0	4	0.8

TABLE 8.8.14.1.2: 2 Incidence of AEs by System-Organ Class in Trial 107.047

System Organ Class	Group I[2]				Group II[3]		Total	
	Direct Entry[1]		Total					
	n	%	n	%	n	%	n	%
Application Site Disorders	3	1.1	10	2.4	0	0	10	2.0
Autonomic Nervous System Disorders	2	0.7	3	0.7	0	0	3	0.6
Body as a Whole - General Disorders	69	24.5	111	26.1	16	24.6	127	25.9
Cardiovascular System Disorders, General	24	8.5	38	8.9	4	6.2	42	8.6
Centr & Periph Nervous System Disorders	45	16.0	63	14.8	3	4.6	66	13.5
Endocrine Disorders	2	0.7	4	0.9	0	0	4	0.8
Gastro-Intestinal Disorders	108	38.3	155	36.5	15	23.1	170	34.7
Hearing and Vestibular Disorders	3	1.1	9	2.1	1	1.5	10	2.0
Heart Rate and Rhythm Disorders	2	0.7	2	0.5	0	0	2	0.4
Liver and Biliary System Disorders	9	3.2	10	2.4	0	0	10	2.0
Metabolic and Nutritional Disorders	21	7.4	31	7.3	3	4.6	34	6.9
Musculo-Skeletal Disorders	35	12.4	44	10.4	5	7.7	49	10.0
Myo Endo Pericardial & Valve Disorders	10	3.5	19	4.5	0	0	19	3.9
Neoplasms	1	0.4	1	0.2	0	0	1	0.2
Platelet, Blooding & Clotting Disorders	3	1.1	3	0.7	0	0	3	0.6
Psychiatric Disorders	21	7.4	30	7.1	4	6.2	34	6.9
Red Blood Cell Disorders	10	3.5	16	3.8	5	7.7	21	4.3
Reproductive Disorders, Female	3	1.1	5	1.2	0	0	5	1.0
Reproductive Disorders, Male	2	0.7	5	1.2	1	1.5	6	1.2
Resistance Mechanism Disorders	13	4.6	25	5.9	1	1.5	26	5.3
Respiratory System Disorders	64	22.7	113	26.6	13	20.0	126	25.7
Skin and Appendages Disorders	30	10.6	57	13.4	6	9.2	63	12.9
Special Senses Other, Disorders	1	0.4	1	0.2	0	0	1	0.2
Urinary System Disorders	41	14.5	66	15.5	6	9.2	72	14.7
Vascular (Extracardiac) Disorders	7	2.5	16	3.8	1	1.5	17	3.5
Vision Disorders	16	5.7	28	6.6	3	4.6	31	6.3
White Cell and RES Disorders	1	0.4	3	0.7	0	0	3	0.6
Total number of patients with one or more adverse events	224		336		48		384	

[1] Direct entry = patients who were not previously enrolled in a meloxicam trial.
[2] Group I = patients treated with meloxicam up to 24 months by either direct- or indirect-entry (indirect-entry included all meloxicam-treated patients from Trial 107.045).
[3] Group II = indirect-entry patients who received meloxicam for up to 18 months (piroxicam patients from

PREGNANCY USE

In this submission there were two pregnancies on meloxicam, one with an apparently healthy baby, and the other unknown.

APPEARS THIS WAY
ON ORIGINAL

This page of the document contains confidential information that will not be included in the redacted portion of the document for the public to obtain.

OVERDOSES

There have been four reported overdoses (2 adults, 2 children; 3 intentional, 1 accidental) involving meloxicam in amounts approximately 6-11 times the highest recommended dose on a mg/kg basis, all of whom recovered. The narratives for these patients are in appendix 12. Cholestryamine has been shown to accelerate clearance of meloxicam.

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CONCLUSIONS

DOSAGES: The 7.5mg and 15mg are appropriate dosages. The 30mg dose was clearly more GI toxic, and this should be noted.

AE TABLES: Three AE comparisons for events occurring at a 2% incidence or greater seem appropriate: (1) Trial #181, (2) Shortterm active-control trials (4: #043,044,153,154) and Six month active-control trials (#045, 063).

GI PARAGRAPH: As with other NSAID labels, the standard GI paragraph will need to be included. The post hoc PUB analyses should not be in the label.

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ON ORIGINAL