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Before the FDA Arthritis Advisory Committee
on the Petition to Ban Piroxicam (Feldene)
October 11, 1995

It has been recently estimated that, among older adults alone, there are 41,000 hospitalizations and 3,300 deaths each year due to ulcer complications such as perforation, bleeding and severe ulcers which are caused by NSAIDs (nonsteroidal antiinflammatory drugs).[1] The overriding public health questions for the FDA and for this committee is what can be done to reduce this toll by using less dangerous drugs such as ibuprofen (Motrin, Advil, Nuprin, etc.) instead of a much more dangerous drug such as piroxicam (Feldene) for those circumstances in which an NSAID is indicated such as rheumatoid arthritis and, secondly, how to lessen the unnecessary use of any of these drugs for circumstances--such as many cases of osteoarthritis--where a pain reliever such as acetaminophen will suffice. In 1993, there were 4.37 million prescriptions for piroxicam filled in retail pharmacies in the U.S.

This is the fourth time in our 24 years that the Health Research Group has petitioned the FDA to ban a widely-used NSAID because, based on our review of the published and unpublished data, it was clear that the dangers of these drugs were so great in comparison to their benefits that there was no reason for them to stay on the market. The first instance was in May 1982 when, weeks after it came on the market, we asked the FDA to ban benoxaprofen (Oraflex) because of its serious liver and kidney toxicity. The drug was withdrawn world-wide in August 1982. The second instance was phenylbutazone (Butazolidin) and the closely related drug, oxyphenylbutazone (Tandearil) which we filed a petition to ban in December 1983, because of serious bone marrow toxicity. Oxyphenylbutazone was taken off the U.S. market several years later and phenylbutazone was allowed to stay on the market with severe restrictions. In 1982, the year before our petition, there were 2.5 million new prescriptions filled for butazolidin but by 1993, the last year for which we have data, there were only 78,000 new prescriptions filled, approximately 3% of the number in 1982. The third NSAID was the pain-killer, suprofen (Suprol) which we petitioned the FDA to ban in September 1986, because it was causing a large number of cases of acute renal failure in people who had no pre-existing illnesses and who were not taking any other drugs. In May 1987, sales were suspended by McNeil, its manufacturer.

In early 1986, we petitioned the FDA to change the label on piroxicam so that it would not be used in people over 60 because of serious concerns we had about its long half-life and subsequent tendency to accumulate in the blood, especially in older people. In addition, there was a disproportionate fraction of spontaneously filed reports to the FDA of ulcer complications, including death, because of piroxicam use in older people. Also,

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[1]Ray WA, Griffin MR, Shorr RI. Adverse drug reactions and the elderly. *Health Affairs* (Millwood) 1990;9:114-22.

internal documents from Pfizer voiced concerns about the drug. In addition, we spoke to a number of gastroenterologists, especially in the United Kingdom, who had seen, among large numbers of patients they had treated for gastrointestinal bleeding and other ulcer complications, a disproportionate amount of piroxicam use. In 1984, the year before our petition, there were 8 million prescriptions filled for piroxicam. Our petition was denied because, as proudly hailed in Pfizer's Feldene ads shortly thereafter, FDA Commissioner Frank Young said that "...properly analyzed epidemiological and spontaneous report data fail to provide evidence of an excess of G.I. toxicity with piroxicam." It is of interest that, even today, in the face of considerably more evidence pointing toward the same direction, further documenting serious risks of piroxicam in comparison to other NSAIDs, Pfizer claims that "the safety profile of piroxicam can not be differentiated from other NSAIDs used as intended..."

The petition we filed in December 1994, to entirely ban piroxicam was largely based on a series of eight published case-control epidemiological studies comparing piroxicam to other NSAIDs, all of which were published after our 1986 petition, including five published in 1993 or 1994. Between the first marketing of piroxicam in 1982 and July 1994, according to data obtained from the FDA, there were 299 deaths reported in people using piroxicam, including 144 people whose deaths were related to serious gastrointestinal (GI) complications such as ulcers, perforations or bleeding.

Interestingly, the basis for our conclusion to now seek a complete ban on piroxicam was voiced in a recent editorial in the British journal *Lancet* which states that:

> *some NSAIDs are unquestionably more toxic to the gut than others....If an NSAID is indicated, the least toxic agent should be given at the lowest effective dose....Piroxicam, and particularly azapropazone [the latter drug not available in the U.S.], stand out as being toxic to the gut."*[2]

In Table 2 of our December 1994 petition (see next page), the risks for peptic ulcer complications (ulcers, perforation or bleeding) with NSAID use ranges between 0.7 and 31.5 times that seen in people not using NSAIDs. For piroxicam exposure, the reported increased risk of peptic ulcer complications ranges from 4.8 to 19.1 times that in people not taking any NSAID.

It can also be seen in *Table 2* that in the six studies in which the risk of piroxicam can be compared to the risk of ibuprofen (the least dangerous drug in the eight studies), the increased risk of GI toxicity with piroxicam (compared to ibuprofen) was 6.8 times higher (Odds ratio of 13.7 for piroxicam and 2.0 for ibuprofen--13.7/2.0=6.8--Langman et al.), 6.2 times higher than ibuprofen (Garcia et al.), 6.9 times higher (Henry et al.), 3.4 times higher (Savage et al.), 2.8 times higher (Griffin et al.), and 7.1 times higher (Kaufman et al.) than ibuprofen.

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[2] Bateman DN. NSAIDs: Time to re-evaluate gut toxicity. *Lancet* 1994;343:1051-2.

The hallmark of the eight case-control studies that were reviewed was the consistency with which piroxicam stood out as an NSAID with a high estimated relative risk.

When limiting the analysis just to drugs available in the United States, in four of the eight studies, piroxicam had the highest risk of severe GI adverse reactions of any NSAID. In three other studies it had the second highest risk and, in one, the third highest risk. These studies involved patients in eight different countries namely the U.S., U.K., Sweden, Spain, New Zealand, Italy, Hungary, and Australia.

In spite of overwhelming evidence in the literature and elsewhere attesting to the excess risk for piroxicam to cause GI ulceration, bleeding and perforation, it is indeed surprising to note that the company and the FDA continue to maintain in the 1995 *Physicians' Desk Reference* that, "Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such [gastrointestinal] reactions".

The only advantage of piroxicam which appears appealing is its once-a-day dosing. Significantly increased toxicity, however, (a predictable concomitant of many long-lasting drugs) is a dangerous price to pay for convenience. Piroxicam should not be used just because of its once-a-day convenience for patients, all of whom could use low doses of other NSAIDs or other safer alternatives to piroxicam.

Since Dr. Marie Griffin, in her presentation this morning, will review the epidemiological studies which provide evidence for the difference in toxicity between piroxicam and other NSAIDs, I will not dwell on this aspect of our petition further.

Piroxicam's Dangerously Steep Dose-Response Curve for Ulcers, Extremely Small Margin of Safety, Long and Variable Half-Life, Enterohepatic Circulation, Wide Variability in Blood Levels from the Same Dose and the Relationships Between These Which Explain its Increased Gastrointestinal Toxicity

The following tables illustrate some of the pharmacokinetic peculiarities of piroxicam which form, in epidemiological parlance, the plausible biological basis for explaining the increased gastrointestinal toxicity it causes in comparison to other NSAIDs.

Margin of Safety of NSAIDs

Drug	Max/Min Rec'dose (mg per day)	Ratio (Max/Min)
Ibuprofen	3200/1200	2.7
Naproxen	1500/500	3.0
Indomethacin	200/75	2.67
Diclofenac	200/100	2.0
Tolmetin	2000/1200	1.67
Ketoprofen	300/200	1.5
Piroxicam	20/20	1

Source: Facts & Comparisons, 1995; Physicians' Desk Reference, 1995

Half-Life Ranges of NSAIDs

Drug	t½ Range (hrs)
Ibuprofen	1.8 to 2.5
Naproxen	12 to 15
Indomethacin	2.6 to 11.2
Diclofenac	1 to 2
Tolmetin	1 to 1.5
Ketoprofen	2 to 4
Piroxicam	30 to 86

Sources: Facts & Comparisons, 1995; Physicians' Desk Reference, 1995; Martindale

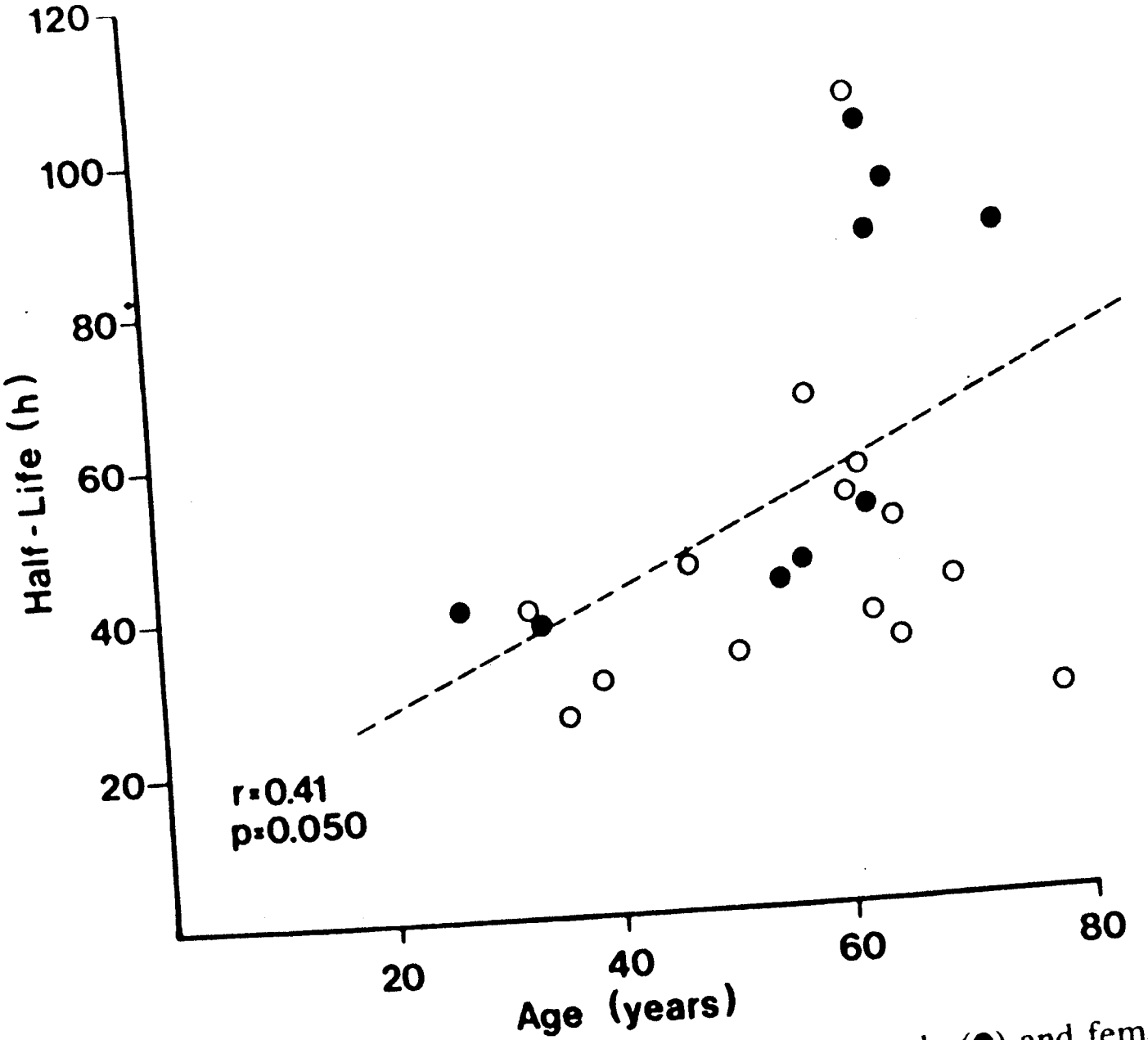

Fig. 2. Effect of age on piroxicam elimination $t_{1/2}$ in male (●) and female (○) patients with RA.

Source: Blocka, et al: J.Rheumatol.1988

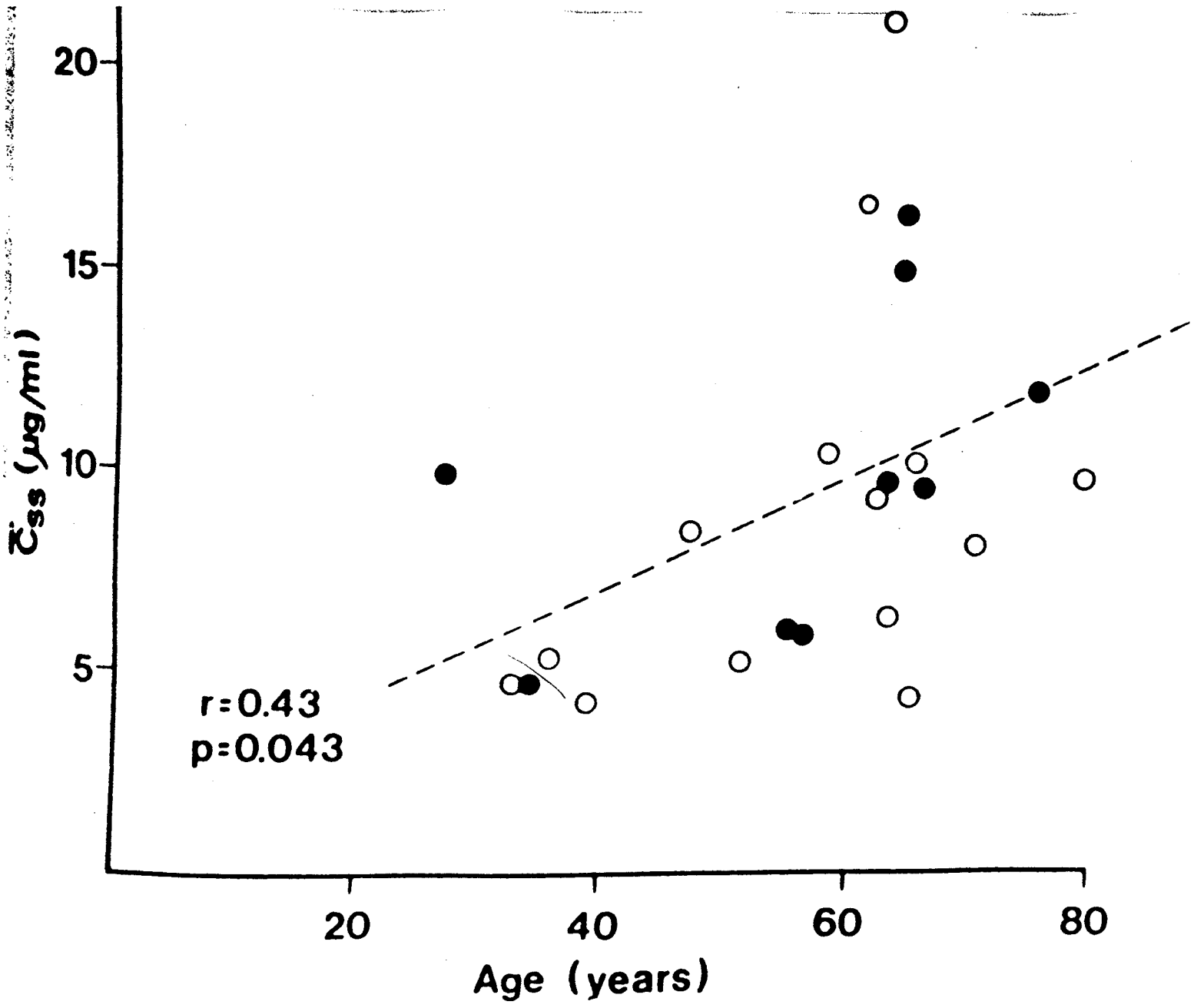

Fig. 1. Effect of age on $\bar{C}_{ss}$ of piroxicam in male (●) and female (○) patients with RA.

Ranges of Piroxicam Steady State Plasma Levels and Half-lifes for Younger and Older Patients

	Age < 60	Age > 60
Css (ug/ml) plasma level)	4.3-11.3	4.3-20.9
t 1/2 (hrs) (half-life)	25.6-65.4	26-104.1

Source: Blocka, et al: J Rheumatol. 1988

Role of Enterohepatic Circulation on Piroxicam Half-Life

	Piroxicam t 1/2 (hours)	
	piroxicam alone	+ cholestyr-amine
1.	50.3 hr	28.1
2.	46.8	28.1
3.	52.3	27.3

Sources: 1. Benveniste, et al, Eur J Clin Pharm. 1990; 2. Guentert, et al, Eur J Clin Pharm. 1988; 3. Ferry, et al, Eur J Clin Pharm. 1990

Human Dose Response Data for Piroxicam

Dose	Incidence of Ulcers
10 mg	0.4% (2/256)
20 mg	1.0% (29/2811)
30 mg	2.8% (21/737)
40 mg	5.9% (22/3720

Source: 1981 Pfizer memo (Dr. N. Pitts) to FDA

Table 2: Estimated Relative Risk (OR) of Peptic Ulcer Complications (Perforations, Ulcers or Bleeding) Associated with Different NSAIDs Observed in Eight Case Control Studies

	Langman et al. OR (95%CI)	Garcia R. et al. OR (95%CI)	Henry et al. OR(95%CI)	Savage et al. OR(95%CI)	Griffin et al. OR(95%CI)	Laporte et al. OR(95%CI)	Kaufman et al. OR(95%CI)[a]	Kaufman et al. OR (95%CI)[b]	Nobili et al. OR (95% CI)
Overall	4.5(3.6-5.6)	4.7(3.8-5.7)	3.0(2.3-3.8)	4.1(2.8-5.9)	4.1(3.5-4.7)	NA	NA	NA	NA
Ibuprofen	2.0(1.4-2.8)	2.9(1.7-5.0)	0.7(0.4-2.4)	1.9(0.5-6.5)	2.3(1.8-3.0)	NA	2.4(0.5-11)	1.1(0.4-2.6)	6.0*(2.9-12.6)
Diclofenac	4.2(2.6-6.8)	3.9(2.3-6.5)	1.7(1.1-2.5)	3.3(1.6-6.9)	NA	7.9(4.3-14.6)	NA	0.9(0.2-4.2)	4.4(2.9-6.7)
Naproxen	9.1(5.5-15.1)	3.1(1.7-5.9)	2.8(1.8-4.3)	5.1(2.4-11.1)	4.3(3,4-5.4)	6.5(2.2-19.6)	9.9(2.3-44)	4.0(1.5-11)	6.0*(2.9-12.6)
Ketoprofen	23.7(7.6-74.2)	5.4(2.6-11.3)	3.6(2.0-6.6)	2.4(1 -5.9)	NA	NA	NA	NA	NA
Indomethacin	11.3(6.3-20.3)	6.3(3.3-12.2)	2.5(1.5-4.1)	13.9(3.3-57.8)	3.8(2.4-6.0)	4.9(2.0-12.2)	1.7(0.2-14)	1.6(0.4-5.9)	9.2(2.9-28.7)
Piroxicam	13.7(7.1-26.3)	18.0(8.2-39.6)	4.8(2 6-8.7)	6.4(2.8-15)	6.4(4.8-8.4)	19.1(8.2-44.3)	17(3.6-79)	18.0(4.1-83)	7.7(2.5-25.7)
Azapropazone	31.5(10.3-96.9)	23.4(6.9-79.5)	NA	NA	NA	NA	NA	NA	NA
Tolmetin	NA	NA	NA	NA	8.5(4.5-16.1)	NA	NA	NA	NA
Meclofenamate	NA	NA	NA	NA	8.7(4.6-16.4)	NA	NA	NA	NA

OR: Odds Ratio
CI: Confidence Interval
NA: Not Available
a: associated with duodenal bleeding
b: associated with gastric bleeding

Conclusion

In conclusion, there is a growing body of data from studies conducted in eight different countries all of which collectively demonstrate piroxicam's greater propensity to cause serious GI bleeding, perforation and ulceration compared to other drugs in its class that are on the U.S. market. In addition, we have reviewed the pharmacokinetic and dose-response (ulcer incidence) data which explain why piroxicam is so dangerous. The evidence presented warrants a ban on piroxicam for people of all ages. Ibuprofen or enteric-coated aspirin are a preferable first choice for most arthritis patients because of their relatively low incidence of serious GI toxicity. If they do not work, there are still a variety of other drugs, safer than piroxicam, which can be tried. (Acetaminophen may be an appropriate alternative for many patients with osteoarthritis since some do not require an antiinflammatory drug.)