

December 5, 1994

CITIZEN'S PETITION

David A. Kessler, MD, JD  
Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

**Citizen's Petition to Withdraw Approval of Piroxicam (Feldene, and generic versions)**

Dear Dr. Kessler:

Based on new information, not available when the drug was originally approved by the Food and Drug Administration (FDA), Public Citizen, a nationwide consumer organization with about 110,000 members, hereby petitions the FDA, pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to remove the nonsteroidal anti-inflammatory drug (NSAID) piroxicam from the market. The drug is marketed as Feldene by Pratt/Pfizer and as piroxicam by Lederle; Mylan; Par; Roxane, and others.

**A. ACTION REQUESTED**

We hereby request that the widely sold arthritis drug piroxicam including Feldene (capsules: 10mg, 20mg; Pratt/Pfizer) and generic versions (Lederle; Mylan; Par; Roxane; and others) be removed immediately from the market. In 1992, according to data from IMS, 5.5 million prescriptions for piroxicam were filled in retail pharmacies in the United States.

**B. STATEMENT OF GROUNDS**

It is well known that treatment with NSAIDs may be associated with serious gastrointestinal (GI) side effects. Several studies have shown that a user of NSAIDs has a three to four times higher risk of upper GI bleeding, perforation, or both than does a non-user.<sup>1,2</sup> Several studies suggest that there may be major differences among the individual NSAIDs with regard to their potential to cause adverse effects.<sup>3,4</sup> In the mid-1980's, three FDA epidemiologists examined adverse reaction reports submitted to FDA for episodes of severe GI toxicity associated with eight different NSAIDs and found that the rate of reports per million prescriptions for piroxicam ranked highest among the eight drugs.<sup>5</sup> However, they concluded - - as it turns out, incorrectly -- that large and clinically important differences in rates of upper GI bleeding, perforation, and ulcer between piroxicam and the rest of the NSAIDs probably did not exist. They admitted that, with more sensitive and accurate studies, piroxicam might prove to be more "ulcerogenic" than other NSAIDs.<sup>5</sup> In 1985, several authors voiced their concern that piroxicam might be associated with a higher risk of upper GI bleeding, perforation, and ulcer compared with other NSAIDs.<sup>6,7,8,9</sup>

As you may be aware, on January 8, 1986, we petitioned the Department of Health and Human Services (DHHS) and the FDA to immediately ban, as an imminent hazard to the public health, the use of piroxicam in people aged 60 and older. Our petition was based on internal documents obtained from the manufacturer of piroxicam, documents from the FDA, a review of published medical literature, and adverse reaction reports of GI ulcers, bleeding, and perforation.

Our petition was denied on the ground that there is "no basis for concluding that piroxicam is more likely to cause serious gastrointestinal toxicity in the elderly than similar products," (Letter of Otis R. Bowen, MD, Secretary, DHHS, July 7, 1986 to Public Citizen).

More recent evidence<sup>3,4,10,11,12,13,14,15</sup>--five studies having been published in 1993 or 1994--strongly suggests that piroxicam has a higher propensity to cause severe GI toxicity than most other NSAIDs. Based on a review of these recent studies, we hereby petition the FDA to immediately ban the use of the popular arthritis drug piroxicam (Feldene, Pratt/Pfizer; and generic versions) in all age groups because it is more dangerous than other NSAIDs now on the market in the U.S.

Interestingly, the basis for our conclusion to 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 US], stand out as being toxic to the gut. It is unclear whether this toxicity represents a higher than necessary licensed dose for these drugs, or whether it is attributable to other pharmacological factors. Nevertheless, the risk-benefit of these agents, especially in the elderly, should be reconsidered by licensing authorities."**<sup>16</sup>

#### **Adverse Reaction Deaths Reported to FDA**

We have obtained data from the FDA's spontaneous adverse drug experience reporting system database concerning deaths in patients who were using piroxicam (See *Table 1*). The FDA's database has received a total of 4,877 adverse drug experience (ADE) reports associated with piroxicam use since the drug was first approved in 1982 through July 1994. This includes a total of 299 deaths in males and females in the age range 12 to 93 years. Of these 299 deaths, 149 (almost 50 percent) occurred in other countries. Age was missing in 57 (approximately 20 percent) ADE reports where death was mentioned as an outcome with piroxicam use. In the remaining 242 reports, 53 fatalities (about 18 percent) occurred in those aged 60 years or less. The majority of deaths (189 or 63 percent) occurred in those over 60 years old.

**Table 1: Major Adverse Drug Experiences that resulted in Deaths with Piroxicam as the suspect drug reported to the FDA between August 1982-July 1994**

Adverse Drug Experiences	Number of Deaths <sup>a</sup>	Age 60 years or less	Age >60 years	Age Unknown
GI Ulcer/Perforation/ Hemorrhage/ Hematemesis/Melena	144 (48%)	14 (10%)	109 (75%)	21 (15%)
Others adverse reactions <sup>b</sup>	155 (52%)	39 (25%)	80 (52%)	36 (23%)

GI = Gastrointestinal

a = Total number of deaths are 299. Each individual death may be coded with up to four terms. Death is not necessarily due to the adverse drug experience.

b = Includes kidney failure/heart arrest/myocardial infarction/hepatitis/heart failure/liver failure/aplastic anemia/agranulocytosis etc.

In spite of the limitations of the spontaneous reporting system data, i.e., only a small fraction of adverse events are reported to the FDA, *Table 1* indicates that approximately half of the deaths (144) may have resulted from serious GI adverse effects (ulcer/perforation/hemorrhage/hematemesis (vomiting of blood)/melena (blood in the stool) of piroxicam. Seventy-five percent of the GI complications-related deaths occurred in those aged above 60 years old. **Because the under-reporting of adverse events is very substantial, the actual number of serious GI complications and deaths associated with piroxicam use is likely to be ten times higher. The 10 to 1 under-reporting ratio is often cited by the FDA itself.**

### Review of Epidemiological Studies

In this section, we review in detail several recently published epidemiological studies which formed the basis of our conclusion that piroxicam should be removed from the market.

There are two epidemiological research designs, cohort and case-control, that have been used to study the risk of severe GI adverse events associated with NSAID therapy. The strongest studies are those that defined cases, controls, outcome, and exposure accurately and reproducibly, thereby adjusting for factors other than differences in drug toxicity which might explain differences in toxicity.<sup>17</sup>

## **Longer Half-Life Means More Dangers**

Concerns have been expressed that piroxicam which is a long-acting agent, might be associated with a higher risk than short-acting agents.

Henry et al. have shown that when individual NSAIDs were ranked by odds ratios (relative risks for GI complications), and plasma half lives (the time it takes to get from the peak blood level to one-half of that level, there was a significant relationship between the estimated relative risks (odds ratios) for GI complications and plasma half lives (Spearman rank correlation coefficient 0.643, P = 0.05). In other words, piroxicam with an average 50 hour half life which is 25 times longer than the two hour half life of ibuprofen, had a 6.9 times higher risk of GI complications than ibuprofen. The authors concluded that taken together with other studies the data reinforces the concern about piroxicam.

Interestingly, the basis for our conclusion to 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 US], stand out as being toxic to the gut."*

## **Other Adverse Effects Associated With Piroxicam**

In addition to the serious GI toxicity, a recent meta-analysis (research that pools data from many different studies) found that piroxicam produced the most marked elevation in blood pressure (6.2 mm Hg; 95% CI 0.8-11.5). This means that patients who are exposed to piroxicam have additional risk of high blood pressure added to the already high risk of life-threatening GI adverse effects.

## **Conclusion**

In conclusion, there is a growing body of data from studies conducted in eight countries all of which 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. The evidence 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. For instance, *acetaminophen* may be an appropriate alternative for many patients with osteoarthritis since some do not require an *anti-inflammatory drug*.

**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) <sup>a</sup>	Kaufman et al. OR (95% CI) <sup>b</sup>	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)
Azaproprazone	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

\*: Naproxen and Ibuprofen combined

**Griffin et al.**<sup>3</sup> conducted a nested case-control study whose goal was to evaluate the relative risk for peptic ulcer disease that is associated with the use of non-aspirin NSAIDs. The study sample was drawn from the Tennessee Medicaid program. They included 1415 patients (cases) who had been hospitalized for either gastric or duodenal ulcer (confirmed by surgery, endoscopy, x-ray, or autopsy) or upper GI hemorrhage (defined by hematemesis, the presence of blood in a nasogastric aspirate, or melena, as determined by review of hospital records) at some point during the study period (1984 through 1986). 7063 controls were selected from Medicaid enrollees who did not meet the study criteria for inclusion. All cases and controls were 65 years of age or older. Exposure was defined with respect to recency of use of NSAIDs. Measure of exposure was a filled prescription for a NSAID as a proxy to actual drug use and may not be a good measurement criteria. The overall estimated relative risk for the development of peptic ulcer disease among current users of NSAIDs, compared with that among nonusers, was 4.1 (95% CI 3.5-4.7) and that associated with piroxicam use was highest 6.4 (95% CI 4.8-8.4) after tolmetin, 8.5 (95% CI 4.5-16.1) and meclofenamate 8.7 (95% CI 4.6-16.4) users. They also found that the risk for the development of ulcer disease increased with increasing dose. The authors did not adjust for previous history of ulcer disease, nonprescription drug use, and social habits (smoking and heavy alcohol use).

**Laporte et al.**<sup>4</sup> examined the risk of upper GI bleeding associated with the use of non-narcotic analgesics and NSAIDs in three hospitals in Spain. Cases were 875 patients who were hospitalized with acute upper GI bleeding with at least one diagnosis of benign gastric ulcer, duodenal ulcer, acute lesions of the gastric mucosa, and erosive duodenitis defined endoscopically or surgically. There were 2682 controls selected from patients admitted with acute clinical disorders unrelated to analgesics or NSAIDs intake. There was no age restriction. Over 50% of cases and controls were 60 years old or less. A detailed structured questionnaire was administered by two specially trained nurses, and two physicians, to ascertain exposure in potential cases and controls soon after admission (within 14 days). The estimated relative risk of GI bleeding associated with aspirin was 7.2 (95% CI, 5.4-9.6) and that for piroxicam use was highest 19.1 (95% CI, 8.2-44.3). The authors took account of previous history of ulcer disease, nonprescription drugs such as aspirin, and social habits (use of caffeine-containing beverages; smoking habit; alcohol consumption).

**Langman et al.**<sup>10</sup> performed a case-control study in the UK to examine if some NSAIDs are more likely to cause peptic ulcer complications than others. They compared previous use of NSAIDs in 1144 patients (cases) who were hospitalized because of GI bleeding with 1126 hospital controls and 989 community controls matched for age and sex. All cases and controls were 60 years of age or older. Exposure was ascertained by standardized questionnaire administered by trained research associates and where possible the information was checked against hospital and general practice records. The overall estimated relative risk for peptic ulcer bleeding with the use of any non-aspirin NSAID during the three months before admission, compared with that among nonusers, was 4.5 (95% CI, 3.6-5.6), and that associated with piroxicam use was third highest 13.7 (95% CI, 7.1-26.3) preceded by azapropazone 31.5 (95% CI, 10.3-96.9) and ketoprofen 23.7 (95% CI, 7.6-74.2). The authors adjusted for previous history of peptic ulcer disease, dyspepsia, smoking, and alcohol use.

**Garcia Rodriguez and Jick**<sup>11</sup> performed a case-control study in the UK, to assess the variation in risk of upper GI bleeding and perforation (UGIB) associated with various individual NSAIDs, with adjustment for the characteristics of use and other independent risk factors (advanced age, smoking, history of peptic ulcer, and use of oral corticosteroids or anticoagulants). The study sample included 1457 cases of (UGIB) and 10,000 controls identified by a general practitioners' computerized records system known as VAMP (Value Added Medical Products) Research (London, UK). Forty-three percent of cases, and 73% of controls were 25 to 59 years old. To ascertain exposure and diagnosis computerized information was checked with paper-based medical records. The overall estimated relative risk for UGIB associated with current use of NSAIDs was 4.7 (95% CI, 3.8-5.7) compared with nonusers, and that associated with piroxicam use was second highest 18 (95% CI, 8.2-39.6) preceded by azapropazone 23.4 (95% CI 6.9-79.5).

**Henry et al.**<sup>12</sup> conducted a case-control study to assess the variability in the risk of major GI complications from NSAIDs. They recruited 644 patients (cases) with UGIB in three hospitals in Australia, and 1268 controls (229 community controls and 1039 hospital controls) most of whom were matched for age and sex. This study was conducted in two phases. In phase 1, only participants aged 60 years or more were included. There was no age limit in phase 2. More than 40% of cases and controls were <65 years old. Exposure ascertainment for both cases and controls was made by a trained nurse who administered a structured interview. Information gathered was checked by consultation with general practitioners and medical records. The overall estimated relative risk for UGIB among users of any NSAID in the previous week was 3.0 (95% CI, 2.3-3.8), and that associated with piroxicam use was the highest 4.8 (95% CI, 2.6-8.7). The authors did control for non-prescribed drug use and social habits.

**Savage et al.**<sup>13</sup> conducted a case-control study in New Zealand to assess the variation in the risk of peptic ulcer complications with NSAIDs. A total of 494 patients presenting with GI hemorrhage or perforation (confirmed by endoscopy, surgery, or postmortem) were selected as cases and compared with 972 hospital controls. The age range of cases was 19 to 98 years. Thirty-three percent of cases were <65 years of age. There were no data on the age breakdown of controls except that cases were matched by age with controls. A standardized questionnaire was administered to ascertain exposure in cases and controls. General practitioners' records and referral letters were used to assess exposure status in those who could not be interviewed. The overall adjusted estimated relative risk for peptic ulcer complications in users of NSAIDs was 4.1 compared to controls, and that associated with piroxicam use was second highest 6.4 (95% CI, 2.8-15.0) preceded by indomethacin 13.9 (95% CI, 3.3-57.8). The authors adjusted for non-prescription drug use and social habits.

**Kaufman et al.**<sup>14</sup> performed a multinational case-control study in the U.S., Sweden, and Hungary in which 335 cases of gastric bleeding were compared with 670 controls, and 239 cases of duodenal bleeding were compared with 489 controls. Participants were confined to individuals from 18 to 79 years of age at the U.S. and Hungarian centers. There was no age restriction at Swedish centers. There was no data on the age breakdown of either cases or

controls except that controls were matched for sex and age. Median age was 62 years for cases of gastric bleeding and 60 years for cases of duodenal bleeding. A standardized questionnaire was used to ascertain exposure in all three countries. For cases, additional information was obtained from hospital records. The estimated relative risk for gastric bleeding for regular (at least once every other day per week) aspirin use was 4.4 (95% CI, 2.9-6.7), and that for piroxicam use was the highest 18 (95% CI, 4.1-83). The estimated relative risk of duodenal bleeding for regular use of aspirin was 7.1 (95% CI, 4.2-12.0), and that for piroxicam use was the highest 17.0 (95% CI, 3.6-79). The authors controlled for non-prescription drug use and social habits.

**Nobili et al.**<sup>15</sup> performed a multicenter case-control study in 14 hospitals in Italy to quantify the risk of upper gastrointestinal bleeding (UGIB) and exposure to NSAIDs. They selected 441 endoscopically confirmed cases of hematemesis (vomiting blood) and/or melena (blood in the stools), and 1323 age and sex-matched hospital controls. There was no age restriction. Fifty-seven percent of cases and controls were <65 years old. All cases and controls were interviewed by the same investigator within each center according to a standardized questionnaire. The overall estimated relative risk for UGIB for users of aspirin in the month preceding hospital admission was 6.6 (95% CI, 4.8-8.9), and that for piroxicam users was the second highest 7.7 (95% CI, 2.5-25.7) preceded by indomethacin 9.2 (95% CI, 2.9-28.7). The investigators adjusted for non-prescription drug use and social habits.

### **Variability in the Risk of GI Toxicity with Individual NSAIDs**

The issue of differing GI toxicity with different NSAIDs would be more definitively answered only with a very large randomized clinical trial.<sup>18</sup> However, such a randomized clinical trial would obviously be impossible to perform, ethically and logistically.<sup>19</sup> All the case-control studies that we examined have collectively suggested an excess risk with piroxicam, confirming earlier concerns by FDA epidemiologists based on increased numbers of adverse GI reports with piroxicam.<sup>5</sup>

As mentioned above, in 1987 FDA epidemiologists predicted that a more careful look at the relative toxicities of these drugs might show that piroxicam is "more ulcerogenic than other NSAIDs."<sup>5</sup>

In spite of overwhelming evidence in the literature attesting to the excess risk for piroxicam to cause GI ulceration, bleeding and perforation, the company and the FDA continue to maintain in the 1994 *Physicians' Desk Reference* that, "Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions".<sup>20</sup>

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 (See section on Pharmacokinetics below). Piroxicam should not be used just because of its once-a-day convenience for patients who could use low doses of other NSAIDs.<sup>21</sup>

With reckless disregard to the lives and health of older Americans in particular, the FDA is continuing to ignore the warnings by the editors of *Medical Letter* more than a decade ago: "Some *Medical Letter* consultants are concerned that piroxicam, the newest NSAID and the one with the longest half-life, might accumulate in elderly patients and cause more gastrointestinal bleeding than other drugs in this class."<sup>22</sup>

### **Criteria for the Causal Nature of an Association**

In order to assess a cause and effect relationship between an exposure and outcome the following criteria have been described<sup>23</sup>:

coherence with existing information or biological plausibility; consistency of the association (replicability of results); time sequence or temporal association; specificity of the association; and strength of the association.

No one of these criteria is absolutely necessary for an association to be causal. And no one of them is sufficient for an association to be considered a causal association. Essentially, the more criteria that are present, the more likely it is that an association is a causal association.<sup>19</sup>

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. In three studies,<sup>4,12,14</sup> piroxicam was associated with the highest estimated relative risk, and piroxicam was second following indomethacin in two studies<sup>13,15</sup> and azapropazone in one.<sup>11</sup> In the remaining two studies piroxicam was associated with the third highest risk preceded by azapropazone and ketoprofen in one<sup>10</sup> and tolmetin and meclofenamate in the other.<sup>3</sup>

**When limiting the analysis just to drugs available in the United States, in four<sup>4,11,12,14</sup> of the eight studies, piroxicam had the highest risk of severe GI adverse reactions of any NSAID. In three<sup>10,13,15</sup> other studies it had the second highest risk and, in one<sup>3</sup>, the third highest risk.**

These studies involved patients in eight countries: the U.S., U.K., Sweden, Spain, New Zealand, Italy, Hungary, and Australia.

A review and meta-analysis (research that pools data from many different studies) of some of the earlier published epidemiological studies concluded that the pooled relative risk for piroxicam was highest.<sup>17</sup> Many of the later studies, with generally improved methodology, show even higher risks.

### **Piroxicam's Pharmacokinetics**

Concerns have been expressed that piroxicam which is a long-acting agent, might be associated with a higher risk than short-acting agents.<sup>7,21</sup> We alluded to piroxicam's dangers to the elderly due to its long half life in our January 8, 1986 petition. We referred to the

Canadian study<sup>24</sup> which showed that some elderly women had markedly elevated blood levels of piroxicam indicating the drug is cleared more slowly in the older population. Although conflicting data are available, the most convincing data suggests that elderly patients, especially women, have significantly higher steady-state levels than younger ones.<sup>25</sup>

"As a broad generalization, drug dosage should be reduced in elderly patients, reflecting the general decline in body function with age. A reduction in dosage is needed particularly in the weak and infirm elderly patient, who often suffers from several diseases, who receives multiple drug therapy, and whose body functions decrease very sharply with advancing years.<sup>26</sup>"

Henry et al.<sup>12</sup> have shown (See *Table 3*) that when individual NSAIDs were ranked by odds ratios (relative risks for GI complications), and plasma half-lives, there was a significant relationship between the estimated relative risks (odds ratios) for GI complications and plasma half-lives (Spearman rank correlation coefficient 0.643, P = 0.05). In other words, piroxicam with an average 50 hour half-life (the time it takes to get from the peak blood level to one-half of that level) which is 25 times longer than the two hour half-life of ibuprofen, had a 6.9 times higher risk of GI complications than ibuprofen. The authors concluded that taken together with other studies the data reinforces the concern about piroxicam.<sup>12</sup>

**Table 3: Estimated relative risks for GI complications associated with the use of individual NSAIDs**

Name of drug	OR (95% CI)	Half life (hr)
Piroxicam	4.8 (2.6-8.7)	50
Ketoprofen	3.6 (2.0-6.6)	8
Naproxen	2.8 (1.8-4.3)	14
Indomethacin	2.5 (1.5-4.1)	3
Sulindac	2.1 (1.1-4.1)	7
Diclofenac	1.7 (1.1-2.5)	1-2
Diflunisal	1.0 (0.4-2.4)	8-12
Ibuprofen	0.7 (0.4-2.4)	2

Adapted from Henry et al.<sup>12</sup>

OR = Odds Ratio

CI = Confidence Interval

## **Age and Piroxicam**

This section reviews the ages of participants in the case-control studies from the available age data. In two studies<sup>3,10</sup> all cases and controls were 60 years of age or older. There was no age limit in the study done by Laporte et al.<sup>4</sup> and more than half of the participants were 60 years old or less. In Garcia Rodriguez and Jick's study<sup>11</sup> 43% of cases and 73% of controls were between the ages of 25 and 59. More than 40% of participants in the study by Henry et al.<sup>12</sup> were less than 65 years old. The age range of cases in another study<sup>13</sup> was 19 to 98 years and 33% of cases were <65 years old. In the study by Kaufman et al.<sup>14</sup> there was no age restriction at one center and participants' ages ranged from 18 to 79 years at the other two centers. In the Italian study<sup>15</sup> 57% of participants were under 65 years old.

Thus, it appears that the increased risk of GI complications such as perforation, ulcer, and bleeding caused by piroxicam are not limited to the elderly.

## **Other Adverse Effects Associated With Piroxicam**

In addition to the serious GI toxicity, piroxicam has been recently reported to be associated with severe, life-threatening liver damage<sup>27,28,29</sup> and aplastic anemia.<sup>30</sup> A recent meta-analysis (research that pools data from many different studies) found that piroxicam produced the most marked elevation in blood pressure (6.2 mm Hg; 95% CI 0.8-11.5) of any of the NSAIDs marketed in the U.S.<sup>31</sup> This means that patients who are exposed to piroxicam have additional risk of high blood pressure added to the already high risk of life-threatening GI adverse effects.

## **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. The evidence presented warrants a ban on piroxicam for people of all ages. Ibuprofen or enteric-coated aspirin are preferable first choices 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.

## **D. ECONOMIC IMPACT STATEMENT**

The requested action will eliminate manufacturers' revenues from the sale of piroxicam products but will increase the sale of relatively safer NSAIDs. This also means substantial savings since hospitalizations associated with piroxicam-induced GI adverse effects will be eliminated. It has been reported that, in patients requiring hospitalizations and surgical interventions, the cost of GI side effects were probably far greater than the lifetime cost of treating the disease for which the NSAID was originally prescribed.<sup>32</sup> The same investigator found that the treatment cost of arthritis increased by 45% when the costs of GI side effects were added.<sup>33</sup>

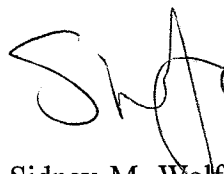
**E. CERTIFICATION**

We certify that, to our best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,



Syed Rizwanuddin Ahmad, MD, MPH  
Staff Researcher



Sidney M. Wolfe, MD  
Director

Public Citizen Health Research Group

## References:

1. Hawkey CJ. Nonsteroidal anti-inflammatory drugs and peptic ulcers: facts and figures multiply, but do they add up? *British Medical Journal* 1990;300:278-84
2. Bollini P, Garcia Rodriguez LA, Perez Gutthann S, Walker AM. The impact of research quality and study design on epidemiologic estimates of the effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract disease. *Archives of Internal Medicine* 1992;152:1289-95
3. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray W. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Annals of Internal Medicine* 1991;114:257-63
4. Laporte JR, Carne X, Vidal X, Moreno V, Juan J. Upper gastrointestinal bleeding in relation to previous use of analgesics and nonsteroidal anti-inflammatory drugs. *Lancet* 1991;337:85-9
5. Rossi AC, Hsu JP, Faich GA. Ulcerogenicity of piroxicam: an analysis of spontaneously reported data. *British Medical Journal* 1987;294:147-150
6. Fok KH, George PJM, Vicary FR. Peptic ulcers induced by piroxicam. *British Medical Journal* 1985;290:117
7. Beermann B. Peptic ulcers induced by piroxicam. *British Medical Journal* 1985;290:789
8. Meyer P, Thijs I. Peptic ulcers induced by piroxicam. *British Medical Journal* 1985;290:789
9. O'Brien JD, Burnham WR. Bleeding from peptic ulcers and use of nonsteroidal anti-inflammatory drugs in the Romford area. *British Medical Journal* 1985;291:1609-10
10. Langman MJS, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RFA, Murphy M, Vessey MP, Colin-Jones DG. Risks of bleeding peptic ulcer associated with individual nonsteroidal anti-inflammatory drugs. *Lancet* 1994;343:1075-78
11. Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual nonsteroidal anti-inflammatory drugs. *Lancet* 1994;343:769-72
12. Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. *Gastroenterology* 1993;105:1078-88
13. Savage RL, Moller PW, Ballantyne CL, Wells JE. Variation in the risk of peptic ulcer complications with nonsteroidal anti-inflammatory drug therapy. *Arthritis and Rheumatism* 1993;36:84-90

14. Kaufman DW, Kelly JP, Sheehan JE, Laszlo A, Wiholm BE, Alfredsson L, Koff RS, Shapiro S. Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clinical Pharmacology & Therapeutics* 1993;53:485-94
15. Nobili A, Mosconi P, Franzosi MG, Tognoni G. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, a post-marketing surveillance case-control study. *Pharmacoepidemiology and Drug Safety* 1992;1:65-72
16. Bateman DN. NSAIDs: time to re-evaluate gut toxicity. *Lancet* 1994;343:1051-2
17. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Annals of Internal Medicine* 1991;115:787-96
18. Willet LR, Carson JL, Strom BL. Epidemiology of gastrointestinal damage associated with nonsteroidal anti-inflammatory drugs. *Drug Safety* 1994;10:170-181
19. Strom BL. Study designs available for pharmacoepidemiology studies. Chapter 2. In: *Pharmacoepidemiology*. ed. Strom BL. Churchill Livingstone, New York, 1989. p.13-26
20. *Physicians' Desk Reference*, 48th edition. Montvale, NJ. Medical Economics Data Production Co;1994:1792-3
21. Wolfe SM. Safety of piroxicam. *Lancet* 1986;ii:808-9
22. Toxicity of nonsteroidal anti-inflammatory drugs. *The Medical Letter on Drugs and Therapeutics* 1983;25:15-16
23. US Public Health Service: *Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service*. US Government Printing Office, Washington, DC, 1964. p.20
24. Richardson CJ, Blocka KLN, Ross SG, Verbeeck RK. Effects of age and sex on piroxicam disposition. *Clinical Pharmacology & Therapeutics* 1985;37:13-8
25. Del Favero A. Anti-inflammatory analgesics and drugs used in rheumatoid arthritis and gout. In: Dukes MNG, Beeley L. *Side Effects of Drugs Annual 12*. Chapter 10. Amsterdam: Elsevier Science Publishers, 1988. p.91-3
26. Rowland M, Tozer TN. Age and weight. Chapter 15. In: *Clinical Pharmacokinetics: Concepts and applications*, 2nd edition. Pennsylvania: Lea & Febiger, 1989. p.5
27. Paterson D, Kerlin P, Walker N, Lynch S, Strong R. Piroxicam induced submassive necrosis of the liver. *Gut* 1992;33:1436-38

28. Hepps KS, Maliha GM, Estrada R, Goodname RW. Severe cholestatic jaundice associated with piroxicam. *Gastroenterology* 1991;101:1737-40
29. Lee SM, O'Brien CJ, Williams R, Whitaker S, Gould SR. Subacute hepatic necrosis induced by piroxicam. *British Medical Journal* 1986;293:540-1
30. Sanada M, Takai K. Aplastic anemia associated with piroxicam. *British Journal of Hematology* 1991;77:256-7
31. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? *Annals of Internal Medicine* 1994;121:289-300
32. Bloom BS. Risk and cost of gastrointestinal side effects associated with nonsteroidal anti-inflammatory drugs. *Archives of Internal Medicine* 1989;149:1019-1022
33. Bloom BS. Cost of treating arthritis and NSAID-related gastrointestinal side effects. *Alimentary Pharmacology and Therapeutics* 1988;2(suppl):131-39



Buyers Up • Congress Watch • Critical Mass • Health Research Group • Litigation Group

Joan Claybrook, President

December 5, 1994

David A. Kessler, M.D., J.D.  
Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Kessler:

The enclosed petition from Public Citizen's Health Research Group urges you, pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355 (e) (3), and 21 C.F.R. 10.30, to remove the dangerous nonsteroidal anti-inflammatory drug (NSAID) piroxicam from the market. The drug is marketed as Feldene by Pratt/Pfizer and as generic piroxicam by Lederle, Mylan, Par, Roxane and others.

In 1992, according to data from IMS, 5.5 million prescriptions for piroxicam were filled in retail pharmacies in the U.S. From the time the drug was first marketed in 1982 until 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.

On January 8, 1986, we petitioned the Department of Health and Human Services and the FDA to ban, as a hazard to the public health, the use of piroxicam in people aged 60 and older. Our petition was denied on the assertion that there is "no basis for concluding that piroxicam is more likely to cause serious gastrointestinal toxicity in the elderly than similar products."

### **Recent Evidence Suggest that Piroxicam Has Higher Risk**

Recent evidence -- five studies having been published in 1993 or 1994 -- strongly suggests that piroxicam has a higher propensity to cause severe GI toxicity than all other NSAIDs marketed in this country.

We have identified eight published case-control studies which examine the risk of severe GI toxicity (bleeding, ulceration, or perforation) associated with individual NSAIDs.



In *Table 2* of the enclosed petition (see attached) the risks for peptic ulcer complications (ulcers, perforation or bleeding) with NSAIDs 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. *No other NSAID was as consistently high in risk as piroxicam.*

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.

The issue of differing GI toxicity with different NSAIDs would be more definitively answered only with a very large randomized clinical trial. However, such a randomized clinical trial would obviously be impossible to perform, ethically and logistically. All the case-control studies that we examined have collectively shown an excess risk with piroxicam, confirming earlier concerns by FDA epidemiologists based on increased numbers of adverse GI reports with piroxicam.

In spite of overwhelming evidence in the literature attesting to the excess risk for piroxicam to cause GI ulceration, bleeding and perforation, it is surprising to note that the company and the FDA continue to maintain in the 1994 *Physicians' Desk Reference* that, "Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions."

The only advantage of piroxicam which appears appealing is its once-a-day dosing. However, significantly increased toxicity (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 who could use low doses of other NSAIDs.

**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) <sup>a</sup>	Kaufman et al. OR (95% CI) <sup>b</sup>	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)
Azaproprazone	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

We identified eight published case-control studies which examine the risk of severe GI toxicity (bleeding, ulceration, and perforation) associated with individual NSAIDs. In order to assess the quality of the studies, we used the checklist of Bollini et al.<sup>2</sup> which addressed methodological issues such as definition of exposure and outcome, control of confounding variables (sex, age, previous ulcer disease), selection biases (diseases likely to be associated with the use of NSAIDs in the control group), and information biases (authors blinded to the case-control status during the patient interview).

*Table 2* gives the estimated relative risk (Odds Ratio) with 95% confidence interval (CI) of peptic ulcer complications associated with individual NSAIDs as observed in the case-control studies that we examined. The risks for peptic ulcer complications with NSAIDs use ranges between 0.7 and 31.5. 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.

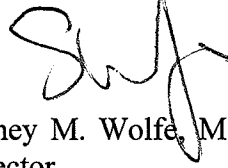
***Table 2* also demonstrates that, in the six studies in which the risk of piroxicam can be compared to the risk of ibuprofen (the least dangerous drug in the studies), the increased risk of GI toxicity with piroxicam (compared to ibuprofen) was 6.8 times higher--Odds ratio of 13.7 for piroxicam and 2.0 for ibuprofen--(Langman et al.<sup>10</sup>), 6.2 times higher (Garcia et al.<sup>11</sup>), 6.9 times higher (Henry et al.<sup>12</sup>), 3.4 times higher (Savage et al.<sup>13</sup>), 2.8 times higher (Griffin et al.<sup>3</sup>), and 7.1 times higher (Kaufman et al.<sup>14</sup>) than ibuprofen. No other NSAID was as consistently high in risk as piroxicam.**

The proof of how dangerously out-of-date the FDA and Pfizer are on the topic of piroxicam is proven by the current labeling which, despite the evidence cited above, states that "Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such [GI] reactions." Nothing could be farther from the truth. We urge you to act as quickly as possible on the enclosed petition in order to spare many Americans from the unnecessarily life-threatening risks of piroxicam.

Sincerely,

A handwritten signature in cursive script that reads "Syed Rizwanuddin Ahmad".

Syed Rizwanuddin Ahmad, M.D.  
Staff Researcher

A handwritten signature in cursive script that reads "Sidney M. Wolfe".

Sidney M. Wolfe, M.D.  
Director