

Petition to Require a Warning on All Fluoroquinolone Antibiotics

August 1, 1996

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Commissioner, Food and Drug Administration
5600 Fishers Lane
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Dear Dr. Kessler:

Based on more than 130 reports of tendon inflammation (many involving rupture), most frequently involving the Achilles tendon, in persons using the widely-prescribed class of antibiotics known as fluoroquinolones, Public Citizen, representing consumers nationwide, hereby petitions the FD.A., pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and C.F.R. 10.30, to add a warning about this serious problem to the label of all fluoroquinolone antibiotics marketed in the United States. These include: ciprofloxacin (Cipro, Bayer Corporation), enoxacin (Penetrex, Rhone-Poulenc Rorer), lomefloxacin (Maxaquin, G.D. Searle), norfloxacin (Noroxin, Merck & Company), and ofloxacin (Floxin, McNeil Pharmaceutical). (In 1995, there were 14.4 million prescriptions filled for these antibiotics in U.S. retail pharmacies according to data from IMS.) In addition, consumers must be warned

through F.D.A. approved MedGuides (patient package inserts) how to recognize and react to this potentially serious adverse effect of fluoroquinolone antibiotics.

Only one fluoroquinolone antibiotic sold in the U.S., ofloxacin (Floxin) (which accounts for less than one-fifth of fluoroquinolone prescriptions), now carries any statement that tendinitis or rupture have been reported with its use, but even this statement is in a part of the label which misleadingly implies that tendon damage may have no relationship to using the drug.⁽¹⁾

Doctors and the public must be warned to immediately discontinue use of fluoroquinolone antibiotics at the onset of tendon pain. The frequency of tendon damage from fluoroquinolones is unknown, but Achilles tendon rupture is a serious condition, often requiring surgical repair Prompt cessation of use of these antibiotics if patients get tendinitis may avoid the progression to frank rupture of the Achilles or other tendons.

Summary Of Evidence

1. In France, 100 patients have been identified who had tendon disorders associated with the use of fluoroquinolone antibiotics, including 31 tendon ruptures.^{(2),(3)}
2. British drug regulatory authorities have received 21 reports of tendon damage associated with fluoroquinolone antibiotics. In 15 of the 21 cases the Achilles tendon was involved. Severity ranged from tendinitis to partial or complete tendon rupture.⁽⁴⁾

3. Doctors in Belgium have reported that out of 230 renal transplant recipients 11 developed an Achilles tendon problem while taking fluoroquinolone antibiotics.⁽⁵⁾

4. In a letter published in January 1995, based on similar reports in F.D.A. files, including tendon ruptures occurring in the United States and published articles, F.D.A staff stated that the agency "will update the labeling [package insert] for all marketed fluoroquinolones to include a warning about the possibility of tendon rupture."⁽⁶⁾

Although F.D.A.'s legal mandate is to protect the public's health, the agency has behaved irresponsibly by failing to take action on a serious problem it has known about for at least 18 months. The situation concerning these drugs is especially dreadful. Despite the fact that the fluoroquinolones are essentially second-line drugs, there being few clinical situations in which they would be the first choice to treat an infection, they are heavily promoted and are often used as first-line drugs in situations where an equally or more effective, less expensive and possibly safer antibiotic would be preferable.

Actions Requested

1. Immediately require a warning in bold type in the official product labeling (package insert) for all fluoroquinolone antibiotics sold in the U.S. (see suggested wording below).
2. Immediately require that a MedGuide (patient package insert) be distributed with all new and refill fluoroquinolone prescriptions warning the public of possible tendon damage and informing the public to stop using the drug and contact their physicians if tendon pain develops (see suggested wording below).

3. Immediately inform all U.S. physicians through a "Dear Doctor Letter" by registered mail about the risk of tendon rupture with fluoroquinolone antibiotics.
4. Immediately inform all other U.S. health professionals through the *F.D.A. Medical Bulletin* about the new warning.

Warning Label for Fluoroquinolone Antibiotics

The following bold warning should be required in the doctor and pharmacist labelling for all fluoroquinolone antibiotics sold in the U.S.:

Tendinitis and rupture have been reported both in the U.S. and abroad from the use of fluoroquinolone antibiotics most frequently involving the Achilles tendon. Reports have also been made involving the rotator cuff (the shoulder), the hand, the long tendon of the biceps and the long extensor of the thumb. This appears to be a rare but potentially serious class effect of fluoroquinolone antibiotics.

This reaction appears to be more common in those treated concurrently with corticosteroids; with increasing age; and in renal transplant recipients but cases have occurred in people without any of these risk factors. Onset of symptoms is sudden and has occurred as soon as 24 hours after beginning treatment. Most patients have recovered completely after one to two months. *The onset of tendon pain calls for immediate withdrawal of fluoroquinolone antibiotics.*

Medication Guide--Informing the Public

It is mandatory that the public have information about this adverse reaction. The public must know when and how to react to protect themselves at the first sign of an adverse drug reaction. Serious tendon damage may be averted only if the patient taking a fluoroquinolone antibiotic stops the drug at the first sign of tendon inflammation.

In its announcement proposing Medication Guides (patient package inserts) to provide prescription drug consumers with comprehensive and reliable drug information, the F.D.A. stated "F.D.A. believes that improved dissemination of information about prescription drug products is necessary to fulfill patients' need and right to be informed." and the F.D.A. would require approved Medication Guides for products "that pose a serious and significant public health concern" requiring immediate distribution of drug information to the public.⁽⁷⁾

The accumulating evidence presented in this petition clearly identifies the fluoroquinolone antibiotics as drugs that pose a significant public health concern.

The following language is suggested for all patient Medication Guides for all fluoroquinolone antibiotics:

The fluoroquinolone family of antibiotics includes: ciprofloxacin (Cipro), enoxacin (Penetrex), lomefloxacin (Maxaquin), norfloxacin (Noroxin), and ofloxacin (Floxin). These drugs have been reported to cause tendon inflammation and sometimes rupture (breakage). Most often this adverse drug effect has involved the Achilles tendon (the tendon running from the heel to the

calf muscle). However, other areas of the body and tendons have also been effected. These include the area of the shoulder known as the rotator cuff, hand, long tendon of the biceps (muscle on the front of the upper arm) and the long tendon at the back of the thumb. This reaction appears to be more common in those people also being treated with oral steroid drugs such as prednisone (Deltasone), prednisolone (Delta-Cortef), dexamethasone (Decadron) and methylprednisolone (Medrol); in older persons; and in renal transplant recipients. But cases have occurred in people who do not fall into any of these three risk categories.

This is a rare but potentially serious adverse effect of all the fluoroquinolone family of antibiotics.

At the first sign of pain or inflammation that might be an indication of tendon damage stop taking the drug to reduce the likelihood that tendon rupture will occur and contact your doctor immediately to discuss the use of an alternative antibiotic. You should refrain from exercise until the diagnosis of tendinitis can be confidently excluded.

Statement of Grounds

Fifteen case reports in the medical literature now describe in detail persons who have suffered tendon inflammation or rupture while taking a fluoroquinolone antibiotic; three of these are in renal transplant recipients. In France, 100 cases have been identified and from the U.K. 21 cases. In Belgium, 11 cases have been reported in renal transplant recipients.

Tables 1 and 2 below outline cases of tendon damage linked to fluoroquinolone antibiotics reported in the medical literature. In Table 2 are the cases of tendon damage in renal transplant recipients who used fluoroquinolones. The case reported is cited, the fluoroquinolone antibiotic implicated is listed along with the reason it was prescribed. After listing the age and gender of the patients, the details of the adverse reaction and the time of onset of symptoms after the drug was started are given.

Table 1 - Case Reports of Fluoroquinolone Tendinitis or Rupture Reported in the Medical Literature

Report	Fluoroquinolone/Dose/Reason for Treatment	Age/Sex	Onset of Symptoms/Clinical Course
Huston (1994) ⁽⁸⁾	Enoxacin 400 mg twice daily for urinary infection	85/M	Symptoms day 7 Bilateral Achilles tendinitis and right tendon rupture on day 14
Borderie et al. (1993) ⁽⁹⁾	Type of fluoroquinolone not stated. Used for septic arthritis of the hip	57/M	Spontaneous rupture of rotator cuff without trauma 28 days after starting treatment
	Type of fluoroquinolone not stated. Used for septic arthritis of the knee	61/M	Spontaneous rupture of rotator cuff without trauma 25 days after starting treatment
Ribard et al.	Pefloxacin ^a 800 mg daily for bladder	49/M	Symptoms after 24 hours Achilles tendinitis and

(1992) ⁽¹⁰⁾	infection		tendon rupture on day 8
	Pefloxacin 800 mg daily to prevent surgical infection	75/M	Symptoms after 24 hours Unilateral Achilles tendinitis only
	Ofloxacin 400 mg daily for bladder infection	86/F	Symptoms after 72 hours Unilateral Achilles tendinitis only
	Pefloxacin 800 mg daily for infection of the vertebrae	68/M	Symptoms at 5 months Bilateral Achilles tendinitis and tendon rupture day 60
	Pefloxacin 800 mg daily for bladder infection	40/F	Symptoms after 48 hours Achilles tendinitis and tendon rupture day 90
	Ofloxacin 400 mg daily for bronchitis	67/M	Symptoms after 8 days Bilateral Achilles tendinitis only
	Pefloxacin 400 mg daily for sore throat	70/M	Symptoms after 5 days Unilateral Achilles tendinitis only
McEwan and Davey (1988) ⁽¹¹⁾	Ciprofloxacin 750 mg twice daily for chest infection	67/M	Symptoms after 3 days Bilateral Achilles tendinitis only

^a *Pefloxacin is not available in the United States*

Table 2 - Case Reports of Fluoroquinolone Associated Tendinitis or Rupture Reported in Renal Transplant Recipients in the Medical Literature

Report	Fluoroquinolone/Dose/Reason for Treatment	Age/Sex	Onset of Symptoms/ Clinical Course
Gillet et al. (1995) ⁽¹²⁾	Norfloxacin 400 mg twice daily for urinary tract infection	40/F	Symptoms after 8 days Inflammation of the long tendon of the thumb
Lee and Collins (1992) ⁽¹³⁾	Ciprofloxacin 500 mg twice daily for abdominal cavity infection	33/M	Symptoms after 4 days Bilateral Achilles tendon rupture
Bailey et al (1983) ⁽¹⁴⁾	Norfloxacin for persistent urinary tract infection. Dose not stated.	56/M	Symptoms after 13 days Bilateral Achilles tendinitis
	Norfloxacin for persistent epididymo-orchitis	34/M	Symptoms after 31 days

	and urinary tract infection. Dose not stated.		Acute pain, tenderness and swelling of tendon of the middle finger, of both hands. Acute pain right ankle and hip
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French Report of Fluoroquinolone Associated Tendinitis or Rupture

Between 1985 and July 1992 100 cases of tendon disorders, including 31 ruptures had been identified in France. The ratio of men to women experiencing a tendon disorder was three-to-one in these cases. Their average age was 63 years and many had received steroid therapy The Achilles tendon was affected most often and half the patients experienced bilateral tendinitis. Other tendons were also involved, such as the long head of the biceps and the long extensor of the thumb. The average time between the start of treatment and the onset of symptoms was 13 days, however in a few patients the tendinitis appeared within one or two days.^{(2),(3)}

Since 1992, French physicians have been informed of the risk of fluoroquinolone induced tendinitis as well as guide-lines to prevent rupture.^{(2),(3)}

British Report of Fluoroquinolone Associated Tendinitis or Rupture

The U.K. Committee On Safety of Medicines (C.S.M.), the British equivalent of the FDA., has received 21 reports of tendon damage associated with fluoroquinolone antibiotics; 11 occurring with ciprofloxacin and 10 with ofloxacin. The reactions reported varied in severity from tendon inflammation to partial or complete

rupture. In 15 of the 21 patients the Achilles tendon was involved. The C.S.M. stated that use of steroids may increase the risk of tendon damage and the adverse reaction appears to be common with increasing age.⁽⁴⁾

Additional cases of tendon damage in patients taking fluoroquinolone antibiotics have been received by the C.S.M. since their original report but the agency has not disclosed the number of such cases. The professional product information (package inserts) for ciprofloxacin, norfloxacin and ofloxacin sold in the U.K. contain clear warnings of the risk of tendon damage.⁽¹⁵⁾

Belgian Report of Fluoroquinolone Associated Tendonitis or Rupture in Renal Transplant Recipients

In Belgium, the records of 230 patients who received renal transplants between January 1, 1991 and December 31, 1992 were reviewed by researchers. Ninety patients were treated at least once with a fluoroquinolone antibiotic and 140 had never received a fluoroquinolone during the study period. In those treated with a fluoroquinolone there were 11 who developed an Achilles tendon problem; 7 with unilateral tendon inflammation, 1 case of unilateral inflammation and subsequent rupture, 2 cases of inflammation of both Achilles tendons, and 1 case of inflammation of both tendons with a single tendon rupture. Overall the incidence of Achilles tendon inflammation and rupture was 7 percent. In the subgroup of patients who were treated with fluoroquinolones, the incidence was 12 percent compared to none in those who had never received a fluoroquinolone antibiotic.⁽⁵⁾

FDA Reports of Fluoroquinolone Associated Tendonitis or Rupture

Through the third quarter of 1995 the F.D.A. had received 52 reports of tendon damage, including 38 ruptures, associated with fluoroquinolone antibiotic use (Table 3 below). The F.D.A.'s data base contains 1,100,000 adverse reaction reports and only 87 reports link any drug to tendon rupture but fluoroquinolone antibiotics accounted for more than 43 percent of these drug-associated tendon rupture cases. In contrast, of these 1,100,000 adverse reaction reports in the FDA data base, 14,067 or only 1.3% were for these five fluoroquinolones. This significant (33-fold) over-representation of fluoroquinolone use among cases of Achilles tendon rupture argues strongly in favor of a causal role of these drugs. Many of the reports in FDA's data base are from foreign countries but some are from the U.S.

Table 3 - Reports of Tendinitis or Rupture with Fluoroquinolone Antibiotics Through the Third Quarter of 1995 - F.D.A. Adverse Drug Reaction Data Base

Fluoroquinolone/ Date Marketed in the U.S.	Total Number of Adverse Reaction Reports	Number of Reports Tendinitis or Rupture	Number of Reports Ruptures Only
Lomefloxacin (Maxaquin) 1992	1,404	1	0
Enoxacin (Penetrex)	59	1	1

1991			
Ofloxacin (Floxin) 1990	4,410	15	7
Ciprofloxacin (Cipro) 1987	6,513	12	9
Norfloxacin (Noroxin) 1986	1,681	23	21
TOTAL	14,067	52	38

Actual Incidence of Fluoroquinolone Associated Tendinitis or Rupture (as opposed to spontaneously/passively reported cases)

Tendinitis or tendon rupture associated with prescription drug use appears to be a rare adverse event. However, a low number of adverse reaction reports may result for one of two reasons. First, the adverse reaction is truly rare. Second, the adverse reaction is grossly under-reported because the association between a drug and an adverse effect seems so unlikely that the adverse event is not attributed to the

drug by prescribers. Assuming that a small number of reports indicates a rare adverse drug reaction can therefore be a dangerous assumption.

A report from the 17th French Pharmacovigilance Meeting illustrates the hazard of making the assumption that an adverse reaction is rare based on the number of adverse reactions spontaneously reported to drug regulatory authorities. The Nancy (France) pharmacovigilance centre studied the frequency of adverse drug reaction reports per 100,000 patients of rheumatological adverse effects of fluoroquinolone antibiotics such as joint pain and tendon damage using three different methods.

Method one was traditional spontaneous reporting. This is the same system used in the U.S. If an adverse reaction is suspected by a health professional the reaction is hopefully reported to the FDA. Method two was "encouraged" reporting in which prescribers were asked by Nancy pharmacovigilance centre if they had observed rheumatological side effects with fluoroquinolones. Method three was termed "reinforced" reporting. Prescribers of fluoroquinolones were identified using prescription records and were asked the same questions about fluoroquinolones by social security authorities.

The reporting of adverse rheumatological effects from fluoroquinolones varied enormously between the three methods. The traditional spontaneous reporting system produced 1 report per 100,000 patients; "encouraged" reporting 18 per 100,000; and the "reinforced" method 342 reports of adverse rheumatological effects — including joint pain and tendon damage — per 100,000 patients⁽¹⁶⁾ Thus, the rate of reports of these adverse reactions to fluoroquinolones was 342 times higher in the group of doctors

identified as having prescribed the drugs and specifically asked if they had observed these adverse reactions.

FDA Inaction

In a January 19, 1995 letter to the *New England Journal of Medicine* F.D.A. staff wrote that the agency knew of 25 cases of tendon rupture, 22 of them occurring outside the U.S. In this letter it was stated on the basis of postmarketing reports and published articles, the F.D.A. "will update the labeling [package insert] for all marketed fluoroquinolones to include a warning about the possibility of tendon rupture." The updated product labeling would also include a recommendation to discontinue treatment with these drugs at the first sign of tendon pain or inflammation and to refrain from exercise until the diagnosis of tendinitis can be confidently excluded.⁽⁶⁾

Conclusion

It is 18 months since F.D.A. staff published their letter and the agency now has at least 38 reports of tendon rupture. This includes 12 reported hospitalizations from fluoroquinolone antibiotics. Yet, nothing has been done to warn doctors, pharmacists or the public about this potentially serious adverse effect. This is irresponsible.

British and French package inserts for the very same drugs warn doctors and pharmacists about the risk of tendon damage. In the rest of Europe, consumers are warned of possible tendon damage from fluoroquinolone antibiotics. European Community regulations now require that prescription drug consumers receive drug information written specifically for them that accurately reflects the same

information given to doctors and pharmacists with each new and refill prescription. Sadly this simple solution--routine patient package inserts for all prescription drugs--to preventing drug induced injury has been denied to U.S. consumers by organized pharmacy and medicine and the drug industry since the early 1980s. Very recently, attempts have been made in Congress to pass legislation which would stop the FDA from implementing programs to increase the number of patient package inserts and thereby allow U.S. consumers to receive objective useful information about prescription drugs.

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,

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