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OFFICE OF THE ATTORNEY GENERAL
STATE OF ILLINOIS

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ATTORNEY GENERAL

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submit this petition under the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to require manufacturers of the fluoroquinolone class of drugs to: 1) revise drug labeling to strengthen warnings of the potential for the serious adverse event of tendonopathy and tendon rupture; 2) create a "black box" warning to reflect the risk and the severity of this adverse side effect; 3) require manufacturers of fluoroquinolone antibiotics to issue a Dear Health Care Professional letter to inform health care providers about this significant hazard to health and announce the changes in drug package labeling; 4) supplement information provided to patients with bolded warnings about the risk of tendonopathy and tendon rupture; and 5) submit the class of fluoroquinolone drugs for review to the FDA's newly established Drug Safety Oversight Board.

A. Action Requested

On behalf of the Office of the Illinois Attorney General, we are writing to you to request action by your agency in regard to a medication side-effect, which although already recognized, is not well-known by practicing physicians and other health care

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professionals. We are referring to the condition of fluoroquinolone-induced tendonopathy, including actual tendon ruptures, which can be multiple, can cause severe and protracted disability, and can require surgical correction. Specifically we request:

1. Revise drug labeling to strengthen warnings of the potential for the serious adverse event of tendonopathy and tendon rupture;

2. Create a "black box" warning to reflect the need to discontinue the use of Fluoroquinolone drugs at the onset of tendon pain. We suggest the use of the following language:

> **Serious tendonopathies including tendon rupture have occurred in patients taking fluoroquinolone antibiotics. The Achilles tendon is most frequently involved but the tendons of the rotator cuff, biceps and hand have been affected. Multiple tendons may be involved and significant disabilities can result. Onset of tendonopathies is highly variable after use of fluoroquinolone antibiotics, varying from onset within 30 days of use, during which frequency is greatest, to several months after cessation of the drug. The risk of tendonitis and tendon rupture is increased in elderly patients, patients on corticosteroids and renal transplant recipients. Patients should be advised to immediately stop the fluoroquinolone at the onset of tendon pain and contact their physician.**

3. Require manufacturers to issue a Dear Health Care Professional letter to inform them about this significant hazard to health and announce the changes in drug package labeling;

4. Supplement information provided to patients with bolded warnings about the risk of tendonopathy and tendon rupture. We suggest the use of the following language:

> **The current family of fluoroquinolone antibiotics includes: ciprofloxacin (Cipro and generics), ofloxacin (Floxin and generics), levofloxacin (Levaquin), gatifloxacin (Tequin), moxifloxacin (Avelox). These medications have been known to cause serious tendonitis (inflammation) and even tendon rupture (breakage). Most often this adverse drug effect has involved the Achilles tendon (the tendon running along the back side of the ankle) but has also involved the tendons of the shoulder, upper arm and hand. This reaction is more**

common in older patients; people on corticosteroids such as prednisone, dexamethasone, prednisilone or methylprednisolone; and patients who have received kidney transplants. However, this complication has also occurred in people who do not fit into any of these categories.

At the first sign of pain or inflammation of a tendon, stop taking the medication and contact your doctor immediately. Refrain from exercise or excessive use of the joint until the diagnosis of tendonitis can be excluded.

5. Finally, we recommend that fluoroquinolone antibiotics be reviewed by the FDA's newly established Drug Safety Oversight Board.

B. Statement of Grounds

Our request for your action has been evoked by the fact that our office has received complaints from Illinois citizens who have suffered significantly from tendonopathies induced by their use of a fluoroquinolone antibiotic, namely Levaquin (Levofloxacin). These complaints motivated our office to conduct an extensive review of the medical literature, and to interview physicians on the staff of academic medical centers, about fluoroquinolone-induced tendonopathies. Our study has led us to conclude that fluoroquinolone-induced tendonopathies are not a rare complication of fluoroquinolone use, and also to realize that this serious side-effect is not adequately appreciated by practicing physicians. Since tendonopathies have been reported as an adverse effect from more than one fluoroquinolone antibiotic, we believe this complication is a therapeutic class characteristic. The current fluoroquinolone antibiotics available in the United States include: ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. We recognize that the drug information documents distributed by the pharmaceutical manufacturers of fluoroquinolone antibiotics do mention that tendonopathy, including tendon rupture, can be caused by fluoroquinolone antibiotics. However, currently this information is buried in lists of potential side effects which are both less frequent and less severe. The prevalence of this serious side-effect, and the inadequate knowledge about it on the part of physicians and other health professionals, prompts us to write to you to ask that a "black-box" warning about fluoroquinolone-induced tendonopathy be required by your agency in all of the pharmaceutical manufacturers' drug information literature. In

addition, we feel it is necessary that your agency require pharmaceutical manufacturers to send a "Dear Health Care Professional" letter to practicing health care providers drawing their attention to this fluoroquinolone complication, such as your agency has appropriately done in regard to other pharmaceuticals in the past. We urge you to rewrite patient information with bolden information warning of this potentially devastating adverse side effect. Finally, fluroquinolone antibiotics should be re-evaluated by the newly established Drug Safety Oversight Board. Besides the risk of tendon rupture, there are other serious issues regarding this class of antibiotics such as cardiac arrhythmias.

We would like to share with you a brief summary of our review of the medical literature:

> Fluoroquinolones are modeled on naxadilic acid, a synthetic antibiotic approved by the U.S. Food and Drug Administration (FDA) in 1963 for the treatment of urinary tract infections.[1] In the 1980s, structural modifications improved their anti-bacterial activity, but also increased their potential toxicity to consumers.[1] In 1992, Abbott Laboratories recalled its drug Omniflox (temafloxacin) after several reports of liver failure and deaths.[2] In 1999, Raxar (grepafloxacin) was taken off the market by Glaxo Wellcome as a result of cardiac arrhythmias and seven deaths.[2] Later that year, the FDA restricted the use of Trovan (trovafloxacin, Pfizer) after more than a dozen reports of acute liver failure, five of which resulted in death.[2]
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> Many adverse drug reactions of fluoroquinolones have been reported. The most common adverse effects are nausea and vomiting, diarrhea, headache, dizziness, rash, and increased sensitivity to the sun.[1] Fluoroquinolone-induced tendonopathy was noted as early as 1983.[3] The first case of a ciprofloxacin-induced tendon rupture was reported in 1987.[4] A pefloxacin-related tendon rupture reported in 1991 led to the published recognition of this complication in the VIDAL (French version of the PDR) in 1992.[5] Prescribers and pharmacists were asked to alert patients and other caregivers to the potential for tendonitis and tendon rupture while taking or after taking antimicrobial fluoroquinolones in a Report of Adverse Events issued by the U.S. FDA in October 1996.[6] The FDA also took steps to revise the package inserts to include a warning of possible tendonitis/tendon rupture.[7] According to the *Southern Medical Journal*, this action was taken "after more than 200 reports of fluoroquinolone-related tendonopathy over a 10-year period."[7] The risk for tendonopathies is increased in patients receiving concomitant corticosteroids, especially in the elderly, according to a warning based on postmarketing surveillance reports, which was added to the PDR in December 2001.[8] In March of 2002, the Italian Health Ministry issued a Dear Doctor Letter in order to

inform physicians of the risk of tendon rupture.[9] According to the Fluoroquinolone Toxicity Research Foundation, Dear Doctor letters were also issued by France and Belgium in 2002.[10]

Fluoroquinolone-induced tendonopathy presents suddenly and is characterized by sharp pain upon walking or with palpation.[7] When tendon ruptures occur it is usually after two weeks of fluoroquinolone therapy;[8] however, they can occur as early as a few hours after the first dose or up to six months after the last dose.[8] Although there is a predilection for the Achilles tendon, shoulder and hand involvement have also been reported.[11]

Severity of the injury directly correlates with the length of treatment.[11] Therefore, timely recognition of fluoroquinolone-induced tendonopathies and immediate discontinuation of fluoroquinolone therapy is a critical first step.[12] Taking either a surgical or conservative approach, tendon rupture still requires casting and prolonged rest.[11] Conservative Achilles tendonitis treatment should include rest, non-steroidal anti-inflammatory drugs, orthotics, cortisone injections, icing, ultrasound, and conventional physical therapy.[11]

Although the exact mechanism underlying fluoroquinolone-induced tendonopathy is poorly understood, a study in *The American Journal of Sports Medicine* suggests that the fluoroquinolone antibiotics alter tendon fibroblast metabolism.[13] In Achilles tendon and shoulder specimens maintained in culture with ciprofloxacin, a study reports a 66% to 68% decrease in cell proliferation and a 36% to 48% decrease in collagen synthesis. Another study reported "necrosis with neovascularization, interstitial edema, and degenerative lesions with fissures but without inflammatory cell infiltrate or angiitis."[7] These clinicians note that most tendon ruptures are at a site of vascular deficiency which suggests that tendon ruptures could be the result of an ischemic process. High dose administration of fluoroquinolones has also been found to cause lesions or cartilaginous erosions in juvenile dogs.[14] The lesions in dog cartilage have caused concern that similar effects might be seen in children.

Postmarketing surveillance has shown a number of factors which increase the risk for tendonitis/tendon rupture.[8] The most commonly reported risk factors are corticosteroid therapy and renal insufficiency.[8,16,17] Other conditions that may predispose a patient to a fluoroquinolone-induced tendon rupture include advanced age, prior tendonopathy, magnesium deficiency, hyperparathyroidism, diuretic use, peripheral vascular disease, rheumatoid arthritis, diabetes mellitus, and strenuous sports activities.[7,8,12]

There have been relatively few studies that have attempted to quantify the incidence of tendonopathy related to the use of fluoroquinolones. A retrospective cohort study published in 1999 in the *British Journal of Clinical Pharmacology* found that during the period from 1995-1996 and based on 1,841 users of fluoroquinolones, the adjusted relative risk of tendonitis from fluoroquinolones was 3.7 for Achilles tendonitis and 1.3 for other types of tendinitis.[17]

A case-control study conducted in the UK between July 1992 and June 1998 and published in the *British Medical Journal* reports the adjusted relative risk of Achilles tendon disorders with current use of fluoroquinolones was 1.9, while the relative risk among patients aged 60 and over was 3.2. Current use was defined as the time patients were on the quinolone plus thirty days. The study also notes that in patients aged 60 and over, concurrent use of corticosteroids and fluoroquinolones increased the risk to 6.2.[16]

A population-based, case-control study, conducted in the UK during the period of 1988-1998 and published in the *Archives of Internal Medicine*, reports the adjusted odds ratio (OR) for Achilles tendon rupture as 4.3 for current exposure to quinolones, 2.4 for recent exposure (30 to 90 days) and 1.4 for past exposure (more than 90 days). The OR of Achilles tendon ruptures was 6 4 in patients 60 to 79 years and 20.4 for patients 80 years and older. [18]

We do appreciate the efforts of the Food and Drug Administration (FDA) to collect and disseminate information about post-approval adverse drug reactions, and we applaud the steps that the FDA has taken in the past to include information about fluoroquinolone-induced tendonopathies in the pharmaceutical manufacturers' information. However, it is our firm belief that the prevalence and severity of this particular drug complication, and the relative lack of knowledge about it among health professionals, warrants a more aggressive educational approach. Consequently, we strongly urge your office to require a "black-box" warning regarding fluoroquinolone-induced tendonopathy in the drug information documents, require manufacturers to send an educational letter to all practicing health professionals about this serious adverse-effect, and to reflect these risks in patient information more accurately and to review fluoroquinolone antibiotics more thoroughly.

We thank you for your consideration of our request, and we hope to receive a letter indicating your response.

C. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

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References

1. Litt JZ. Fluoroquinolones. *South Med J.* 2000; 73: 525.

2. Gebhart F. Calls mount for black box warning on fluoroquinolones. *Drug Topics* 2004; 148: 43.

3. Bailey RR, Kirk JA, Peddie BA. Norfloxacin-induced rheumatic disease [letter]. *N Z Med J* 1983; 96:590.

4. McEwan SR & Davey PG. Ciprofloxacin and tenosynovitis [letter]. *Lancet* 1988; 2: 900.

5. Zabraniecki L, Negrier I, Vergne P, et al. Fluoroquinolone-induced tendinopathy: report of 6 cases. *J Rheumatol* 1996; 23: 516-20.

6. Food and Drug Administration: *Reports of Adverse Events With Fluoroquinolones*. 1996; 26:3.

7. Harrell RM. Fluoroquinolone-induced tendinopathy: what do we know? *South Med. J* 1999; 92; 622-5.

8. Gold L and Igra H. Levofloxacin-Induced Tendon Rupture: A Case Report and Review of the Literature, *J of Amer Board of Fam Prac* 2003; 16: 458-460.

9. Italian Dear Doctor Letter at http://www.ministerosalute.it/imgs/C_17_notaInf_28_listaFile_itemName_0_file.pdf

10. The Fluoroquinolone Toxicity Research Foundation website at http://www.fqresearch.org/dear_doctor_archives.htm. (This foundation appears to be an advocacy group established by those effected by these drugs.)

11. Physicians' desk reference. Montvale, NJ: Medical Economics Co, 56th ed, 2002. Levaquin, p. 2537-43.

12. Gabutti L, Stoller R, Marti HP. Fluoroquinolones as etiology of tendinopathy. *Ther Umsch* 1998; 55: 558-61.

13. Williams, RJ, Attia E., Wickiewicz TL, Hannafin JA. The effect of ciprofloxacin on tendon, paratendon, and capsular fibroblast metabolism. *Am J of Sports Med* 2000; 28: 364-9.

14. Schluter G. Ciprofloxacin: review of potential toxicologic effects. *Am J. Med* 1987; 82(suppl 4A):91-93.

15. Medwatch. Summary of safety-related drug labeling changes approved by FDA center for drug evaluation and research (CDER). Levaquin. Washington, DC: United States Food and Drug Administration; 2001 Dec. Available at: URL: http://www.fda.gov/medwatch/safety/2001/dec01.htm#levaqu

16. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HG, Stricker BH. Fluoroquinolones and risk of Achilles tendon disorders: case control study. *BMJ* 2002; 324: 1306-7.

17. van der Linden PD, van de Lei J, Nab HW, Knol A, Stricker BHCh. Achilles tendinitis associated with fluoroquinolones. *Br J Clin Pharmacol* 1999; 48: 433-437.

18. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HM, Rowlands S, Sricker BH. Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 2003; 163(15):1801-1807.