

June 18, 2014

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

2014 JUN 23 P 2:01

CITIZEN PETITION

RE: Licensed Name: Levaquin
Active Ingredient: Levofloxacin
NDA 020634
Manufactured by Johnson & Johnson (Janssen Pharmaceuticals)
License Date: 12/20/1996

The Southern Network on Adverse Reactions (SONAR), submits this Citizen Petition (Petition) under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA). SONAR requests that the Commissioner of the Food and Drug Administration (FDA) require changes in the professional labeling for Levaquin in order to specify a more accurate benefit/risk profile for this antibiotic.

A. ACTION REQUESTED

This Petition requests that the FDA change the professional labeling for Levaquin under Section 505(o)(4) to FDCA or other appropriate FDCA section(s), in response to new safety information. This action will also strengthen the quality of the Levaquin science base and decisions based on it.

Specifically, SONAR requests the following changes to the Levaquin label:

1. Add "Possible Mitochondrial Toxicity" to the Levaquin Label

It is requested that the following be added to Section 5 of the Levaquin label, "Warnings and Precautions":

FDA-2014-P-0856

CP
2014-5508

Possible Mitochondrial Toxicity

Fluoroquinolones, including Levaquin, may cause Mitochondrial Toxicity due, in part, to an insufficiency of ATP. Mitochondrial conditions that are due to an insufficiency of ATP include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress generated by reactive oxygen species (ROS) related to Mitochondrial Toxicity. Peripheral neuropathy, hepatotoxicity, glucose disturbances, and phototoxicity may result from Mitochondrial Toxicity.

2. Add a Black Box Warning to the Levaquin Label Regarding "Possible Mitochondrial Toxicity"

It is requested that a Black Box Warning be added to the Levaquin label regarding "Possible Mitochondrial Toxicity" as follows:

WARNING: POSSIBLE MITOCHONDRIAL TOXICITY

Fluoroquinolones may cause Mitochondrial Toxicity. Mitochondrial Toxicity has been implicated in conditions such as peripheral neuropathy, hepatotoxicity, glucose disturbances, phototoxicity, developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, lactic acidosis, Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS).

3. Based on the severity of "Possible Mitochondrial Toxicity," SONAR requests:

- a. Levaquin label changes be made immediately.**
- b. "Dear Doctor" letters be distributed regarding Levaquin label changes and requesting that physicians inform patients about the potential impact of "Possible Mitochondrial Toxicity" if they were previously prescribed this drug.**

B. STATEMENT OF GROUNDS

The "ACTIONS REQUESTED" are based on information in the April 17, 2013 FDA document, "Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology" which identified the "Subject" as, "Disabling Peripheral Neuropathy Associated

with Systemic Fluoroquinolone Exposure.” This document was signed by Acting FDA Division Director, Min Chu Chen, RPh, MS, and other FDA staff.

- The Reviewers for this document were Debra Boxwell, PharmD, Safety Evaluator and Jane Gilbert, MD, PhD, Medical Officer;
- Team Leaders were Kelly Cao, PharmD, and Allen Brinker, MD, MS;
- Product Names/Sponsors were six fluoroquinolones, including Levaquin (levofloxacin)—Janssen Pharmaceuticals. (FDA, 2013, page 1)

Section 2.3.2, Table 5 of this FDA document is titled, “Literature Search Strategy for Mechanism of Action.” “Search Terms” include “mitochondria,” “mtDNA,” “oxidative stress,” and “apoptosis.” Literature was searched from January 1980 to December 2012. (FDA, 2013, page 6)

Section 3.3.2 of this FDA document is titled, “Possible Mechanism of Action: Mitochondrial Toxicity,” and explains:

“Fluoroquinolones have been found to affect mammalian topoisomerase II, especially in mitochondria. In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin caused a loss of mitochondrial DNA (mtDNA), resulting in a decrease of mitochondrial respiration and an arrest in cell growth.” (FDA, 2013, pages 11-12)

“Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like Parkinson’s, Alzheimer’s and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress.” (FDA, 2013, page 12)

Section 8.6 of this FDA document is titled, “Possible Mechanism of Action: Mitochondrial Toxicity,” and explains:

“In vitro studies in drug-treated mammalian cells found that nalidixic acid and ciprofloxacin caused a loss of mitochondrial DNA (mtDNA), resulting in a decrease of mitochondrial respiration and an arrest in cell growth. Further analysis found protein-linked double-stranded DNA breaks in the mtDNA from ciprofloxacin-treated cell, suggesting that ciprofloxacin was targeting topoisomerase II activity in the mitochondria.” (FDA, 2013, page 24)

"An oxidative phosphorylation (OXPHOS) system is found on the inner membrane of the mitochondrion and it provides approximately 95% of the energy (ATP) requirements of the cell. The mitochondrial respirator chain is a major producer of oxidative stress, which occurs when there is a greater production of reactive oxygen species (ROS) than antioxidative processes. Approximately 1-4% of oxygen reacting with the respiratory chain is incompletely reduced to the superoxide radical ion, hydrogen peroxide, lipid peroxides, and other free radicals. Under normal circumstances, there is a mechanism to remove or prevent the generation of ROS to avoid cellular damage such as lipid peroxidation, mtDNA mutations, and DNA strand breaks; if this does not happen, it can lead to even more oxidative damage." (FDA, 2013, page 24)

"Mitochondrial conditions that are due to an insufficiency of ATP, especially in organs that rely on mitochondria for their energy source, include developmental disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (ALS) have been associated with the loss of neurons due to oxidative stress generated by ROS.... The phototoxic effects of fluoroquinolones were found to be due to the mitochondrial formation of a singlet oxygen (O₂) and superoxide anion (O₂⁻)." (FDA, 2013, pages 24-25)

"Another study saw damaged mitochondria within 1-2 hours of exposure to elevated glucose." (FDA, 2013, page 25)

Section 8.6 of this FDA document is titled, "Possible Mechanism of Action: Mitochondrial Toxicity." In addition to providing information about "Mitochondrial Toxicity," this section discusses fluoroquinolone drugs already removed from the market due to toxicity as follows:

"Trovaflaxacin was withdrawn from the market in 2001 due to cases of liver failure. Studies in cultured hepatocytes identified the mitochondria as the source of trovaflaxacin's hepatotoxicity. (FDA, 2013, page 25)

"Gatifloxacin was withdrawn from the market in 2006 because of severe glucose disturbances. ...An in vitro study found that high glucose resulted in excessive ROS and mitochondrial dysfunction, which result in a high frequency of Schwann cell apoptosis. Intermittent high glucose also produces a significantly higher percentage of oxidative stress and apoptosis in Schwann cells than constant high glucose. A study done in type 2 diabetic mice saw that with an increase in extracellular glucose, there was excessive mitochondrial fission; this was thought to result in dorsal root ganglia (DRG) neuron oxidative stress and neuronal injury, or activation of the caspase cascade, leading to programmed cell death. Another study saw damage mitochondria with 1-2 hours of exposure to elevated glucose." (FDA, 2013, page 25)

It should be noted that Levaquin has "class effect" with other fluoroquinolones, as indicated in numerous sections of the Levaquin label, in multiple label versions, over the past decade.

(Drugs@FDA, 2014) Additionally, Levaquin's "class effect" with other fluoroquinolones is described in the 12/20/1996 "Levaquin Approval Document" submitted to the FDA by Johnson & Johnson. (Drugs@FDA, 2014). It is assumed, based on these sources, that Levaquin has class effect with Trovafloxacin and Gatifloxacin, both of which were removed from the market due to Mitochondria Toxicity as described in this FDA 2013 document. (FDA, 2013, page 25)

Section 7 of this FDA document is titled, "References," and lists studies used in this FDA document. The following are references which are identified by the FDA as being relevant to "Possible Mitochondrial Toxicity" associated with fluoroquinolones, including Levaquin.

REFERENCES (corresponds in order with references 4-20 on the original FDA document)

1. Rawi SM, Mourad IM, Arafa NMS, Alazabi NI. Effect of ciprofloxacin and levofloxacin on some oxidative stress parameters in brain regions of male albino rats. *Afr J Pharm Pharmacol* 2011;5(16):1888-97.
2. Lawrence JW, Claire DC, Weissig V, Rowe TC. Delayed cytotoxicity and cleavage of mitochondrial DNA in ciprofloxacin-treated mammalian cells. *Mol Pharmacol* 1996;50(5):1178-88.
3. Nadanaciva S, Will Y. New insights in drug-induced mitochondrial toxicity. *Curr Pharm Des* 2011;17:2100-12.
4. Fang C, Bourdette D, Banker G. Oxidative stress inhibits axonal transport: implications for neurodegenerative diseases. *Mol Neurodegener* 2012;7:29.
5. Hulgán T, Haas DW, Haines JL, et al. Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS clinical trials group study. *AIDS* 2005;19(13):1341-9.
6. Kondapi AK, Mulpuri N, Mandraju RK, et al. Analysis of age dependent changes of topoisomerase II α and β in rat brain. *Int J Devl Neuroscience* 2004;22:19-30.
7. Champoux JJ. DNA topoisomerases: structure, function, and mechanism. *Ann Rev Biochem* 2001;70:369-413.
8. Tiwari VK, Burger L, Nikolettópoulou V, et al. Target genes of topoisomerase II β regulate neuronal survival and are defined by their chromatin state. *Proc Natl Acad Sci USA* 2012;109(16):E934-43.
9. Leung GPH. Iatrogenic mitochondrialopathies: a recent lesson from nucleoside/nucleotide reverse transcriptase inhibitors. *Adv Exp Med Biol* 2012;942:347-69.

10. Lenaz G, Bovina C, Formiggini G, Castelli GP. Mitochondria, oxidative stress, and antioxidant defences. *Acta Biochimica Polonica* 1999;46(1):1-21.
11. Kohler JJ, Lewis W. A brief overview of mechanisms of mitochondrial toxicity from NRTIs. *Environ Mol Mutagen* 2007;48:166-72.
12. Bhanu MU, Kondapi AK. Neurotoxic activity of a topoisomerase-I inhibitor, camptothecin, in cultured cerebellar granule neurons. *Neurotoxicology* 2010;31:730-7.
13. Talia V, Veerareddy PR. Oxidative stress induced by fluoroquinolones on treatment for complicated urinary tract infections in Indian patients. *J Young Pharm* 2011;3(4):304-9.
14. Sun LQ, Zhao J, Zhang TT, et al. Protective effects of salvianolic acid b on Schwann cells apoptosis induced by high glucose. *Neurochem Res* 2012;37:996-1010.
15. Sun LQ, Chen YY, Wang X, et al. The protective effect of alpha lipoic acid on Schwann cells exposed to constant or intermittent high glucose. *Biochem Pharmacol* 2012;84:961- 73.
16. Vincent AM, Edwards JL, McLean LL, et al. Mitochondrial biogenesis and fission in axons in cell culture and animal models of diabetic neuropathy. *Acta Neuropathol* 2010;120:477-89.
17. Vincent AM, Edwards JL, Sadidi M, Feldman EL. The antioxidant response as a drug target in diabetic neuropathy. *Curr Drug Targets* 2008;9:94-100.” (FDA, 2013, pages 14-15)

SUMMARY:

The FDA-identified

“Possible Mechanism of Action: Mitochondrial Toxicity”

Warrants a heading under the ‘Warnings and Precautions’ label section,

As well as, a Black Box Warning.

The seriousness of “Mitochondrial Toxicity” requires both of these label changes.

C. ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. 25.22 and 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. 10.30(b), SONAR provides data concerning the economic impact of the requested changes.

The following table outlines the FDA Adverse Event Reporting System (FAERS) data regarding the three most widely prescribed fluoroquinolones: Levaquin, Cipro, and Avelox.

FDA Adverse Event Reporting System (FAERS) November 1, 1997 – February 3, 2011			
	Levaquin	Cipro	Avelox
Total Reactions Reported	79,328	67,498	57,821

As indicated, there were 79,328 Levaquin Adverse Events reported from November 1, 1997 – February 3, 2011. It is estimated that only 1% to 10% of Adverse Events are actually reported to FAERS. Therefore, the following represents the estimated range of actual Levaquin Adverse Events.

FDA Adverse Event Reporting System (FAERS) November 1, 1997 – February 3, 2011		
Levaquin Adverse Events Actual Reported	Levaquin Adverse Events Assuming Only 10% Were Reported	Levaquin Adverse Events Assuming Only 1% Were Reported
79,328	793,280	7,932,800

Because “Mitochondrial Toxicity” can cause such widespread symptoms and is associated with a wide range of neurological disorders, e.g., “disorders of the brain, optic neuropathy, neuropathic pain, hearing loss, muscle weakness, cardiomyopathy, and lactic acidosis. Neurodegenerative diseases, like Parkinson’s, Alzheimer’s and amyotrophic lateral sclerosis (ALS) have been associated with...” (FDA, 2013, page 12), it is challenging to specifically identify the number of adverse events linked directly to “Mitochondrial Toxicity.”

In the Levaquin FAERS data referenced above from November 1, 1997 – February 3, 2011, the top five reported adverse events are related to tendon issues. The next nine Levaquin reported adverse events are ones which may, or may not, be related to “Mitochondrial Toxicity” and are described as follows:

Levaquin FDA Adverse Event Reporting System (FAERS) November 1, 1997 – February 3, 2011	
Potential Mitochondrial Toxicity Adverse Event Reported	Percent of Total Adverse Events Reported
Dyspnoea	4%
Insomnia	4%
Myalgia	4%
Pain	4%
Dizziness	3%
Nausea	3%
Gait disturbance	3%
Asthenia	3%
Pyrexia	3%

The total percentage of Levaquin reported Adverse Events for just these nine potential Mitochondrial Toxicity Adverse Events is **31%**. While conclusions cannot be made regarding whether this 31% is related to “Mitochondrial Toxicity,” the economic impact of treating this 31% of the identified Adverse Events is significant. The next sections estimate the direct medical care cost of just three of these Potential Levaquin Mitochondrial Toxicity Adverse Events: “Insomnia,” “Pain,” and “Gait Disturbance.”

Insomnia. The estimated annual cost of medical care for insomnia per person is \$2,800. (“Waking Up to the Insomnia Crisis.” Sanofi-aventis, 2009, page 8) This does not take into account the societal cost of lost work performance.

Levaquin FDA Adverse Event Reporting System (FAERS) November 1, 1997 – February 3, 2011			
	“Insomnia” Actual Reported (4%)	“Insomnia” Assuming Only 10% Were Reported	“Insomnia” Assuming Only 1% Were Reported
4% of Reported Adverse Events are “Insomnia”	3,173	31,730	317,300
Estimated Annual Direct Cost to Treat “Insomnia” per Person: \$2,800	Estimated Cost: \$8,884,400	Estimated Cost: \$88,844,000	Estimated Cost: \$888,440,000

Painful Neuropathic Disorder (PND). The estimated annual cost of medical care for "Painful Neuropathic Disorder (PND)" per person is \$17,000. (Berger A, Dukes, EM, Oster, "Clinical characteristics and economic costs of patients with painful neuropathic disorders." Journal of Pain, April 5, 2004)

Levaquin FDA Adverse Event Reporting System (FAERS) November 1, 1997 – February 3, 2011			
	"Pain" Actual Reported	"Pain" Assuming Only 10% Were Reported	"Pain" Assuming Only 1% Were Reported
3% of Reported Adverse Events are "Pain"	2,380	23,800	238,000
Estimated Annual Direct Cost to Treat Painful Neuropathic Disorder (PND) per Person: \$17,000	Estimated Cost: \$40,460,000	Estimated Cost: \$404,600,000	Estimated Cost: \$4,046,000,000

Gait Disturbance. The estimated annual cost of medical care for "Gait Disturbance" per person is at least \$10,043, if it is caused by Parkinson's Disease. (Chen, Jack, "Parkinson's Disease: Health-Related Quality of Life, Economic Cost, and Implications of Early Treatment." American Journal of Managed Care, March 17, 2010) Indirect costs for "Gait Disturbance" per person is estimated at \$9,135, if it is caused by Parkinson's Disease.

Levaquin FDA Adverse Event Reporting System (FAERS) November 1, 1997 – February 3, 2011			
	"Gait Disturbance" Actual Reported	"Gait Disturbance" Assuming Only 10% Were Reported	"Gait Disturbance" Assuming Only 1% Were Reported
3% of Reported Adverse Events are "Pain"	2,380	23,800	238,000
Estimated Annual Direct Cost to Treat Painful Neuropathic Disorder (PND) per Person: \$10,043	Estimated Cost: \$23,902,340	Estimated Cost: \$239,023,400	Estimated Cost: \$2,390,234,000

As noted, it is not possible to conclude whether the aforementioned nine Levaquin reported Adverse Events totaling 31% are, or are not, related to "Mitochondrial Toxicity." The total cost to treat potential "Mitochondrial Toxicity" Adverse Events, however, is clearly significant.

Furthermore, it should be noted that Levaquin is sometimes the clinically most appropriate drug of choice. Some of these potential "Mitochondrial Toxicity" Adverse Events, therefore, were not preventable. In other circumstances, however, if there had been Warnings, including a Black Box Warning, about the potential for Levaquin "Mitochondrial Toxicity," some physicians may not have prescribed Levaquin for some patients. Thus, the direct medical care cost and indirect cost to treat these Levaquin Adverse Events could have been reduced. Given that many of these individuals were most likely enrolled in Medicare and Medicaid, this could significantly reduce the overall cost of these government-funded programs.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information and view on which the Petition relies, and that it includes representative data and information known to the Petitioner, which are unfavorable to the Petitioner.

Respectfully yours,

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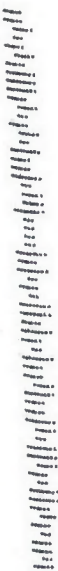
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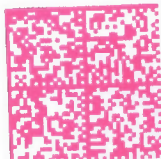
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