September 8, 2014

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

CITIZEN PETITION

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

Southern Network on Adverse Reactions (SONAR), submits this Citizen Petition (Petition) under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 355(o)(4)) and 21 C.F.R. 10.30. 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) of 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, we request the following changes to the Levaquin label:

1. **Require additional Psychiatric Adverse Events to the Levaquin label**

It is requested that the following Levaquin Psychiatric Adverse Events be added to the drug label:

> ***Feeling abnormal, loss of consciousness, disorientation, agitation, delirium, depressed level of consciousness, amnesia, coma, disturbance in attention, panic attack, memory impairment, and nervousness.***

2. Require a "Psychiatric Effects" heading under "Warnings and Precautions"

It is requested that a specific "Psychiatric Effects" heading be added under the "Warnings and Precautions" section of the Levaquin label rather than listing Levaquin Psychiatric Adverse Events under the "Central Nervous System Effects" heading, as is currently done. It is requested that the following "Psychiatric Effects" section be added to the Levaquin label.

> ***Psychiatric Effects***
>
> ***Serious psychiatric events including, toxic psychoses, restlessness, anxiety, confusion, hallucinations, paranoia, depression, nightmares, insomnia, suicidal thoughts or acts, feeling abnormal, loss of consciousness, disorientation, agitation, delirium, depressed level of consciousness, amnesia, coma, disturbance in attention, panic attack, memory impairment, and nervousness have been reported in patients receiving fluoroquinolones, including Levaquin. These events may start during treatment or may be delayed and start days, weeks, or months after the last dose.***

3. Require the following Psychiatric Adverse Events to the Black Box Warning

It is requested that the following language regarding Psychiatric Adverse Events be added to the current Black Box Warning on the Levaquin label:

> ***WARNING: SERIOUS PSYCHIATRIC EVENTS***
> ***Serious psychiatric events including, toxic psychoses, hallucinations, paranoia, suicidal thoughts or acts, loss of consciousness, delirium, depressed level of consciousness, amnesia, coma, and memory impairment have been reported in patients receiving fluoroquinolones, including Levaquin. These events may start during treatment or may be delayed and start days, weeks, or months after the last dose.***

B. STATEMENT OF GROUNDS

Statement of Grounds for Requested Action 1: Add additional Psychiatric Adverse Events to the Levaquin label

The following table lists Levaquin Psychiatric Adverse Events from the FAERS data. The highlighted symptoms are serious Psychiatric Adverse Events, but are not listed on the Levaquin label under "Warnings and Precautions." It is requested that these additional Psychiatric Adverse Events be added to the Levaquin label.

Levaquin FAERS Psychiatric Adverse Events Compared with the Current Levaquin Label		
Adverse Event	**% of Levaquin FAERS Reports Containing this Adverse Event 11/1997 – 6/2012**	**Is this Adverse Event on the Current Levaquin Label under "Warnings and Precautions"?**
Insomnia	4.1%	Yes
Anxiety	3.0%	Yes
Depression	2.7%	Yes
Confusional state	2.2%	Yes
Feeling abnormal	1.7%	No
Loss of consciousness	1.4%	No
Hallucination	1.3%	Yes
Disorientation	.8%	No
Nightmare	.8%	Yes
Agitation	.7%	No
Delirium	.7%	No
Depressed level of consciousness	.7%	No
Psychotic disorder	.7%	Yes
Amnesia	.6%	No
Coma	.6%	No
Disturbance in attention	.6%	No
Panic attack	.6%	No
Memory impairment	.5%	No
Nervousness	.5%	No
Suicidal ideation	.5%	Yes
Restlessness	.5%	Yes

Statement of Grounds for Requested Action 2: Add a "Psychiatric Effects" heading under "Warnings and Precautions"

Psychiatric Adverse Events are not currently listed under a specific "Psychiatric Effects" heading under "Warnings and Precautions" on the Levaquin label. Instead, Levaquin Psychiatric Adverse Events are currently embedded under the label heading, "Central Nervous System Effects" as illustrated below.

> "5.6 Central Nervous System Effects
> Convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving fluoroquinolones, including LEVAQUIN® . Fluoroquinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts…." (Drugs@FDA, 2014)

Because Levaquin Psychiatric Adverse Events are serious and have a significant impact on quality of life, they deserve a specific heading under the "Warnings and Precautions" section of the label. It is requested that a specific "Psychiatric Effects" heading be added under "Warnings and Precautions."

Statement of Grounds for Requested Action 3: Add a Psychiatric Adverse Events Black Box Warning

As described in the October 2011 FDA "Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling" document:

> "A boxed warning is ordinarily used to highlight for prescribers… an adverse reaction so serious in proportion to the potential benefit from the drug…that it is essential that it be considered in assessing the risks and benefits of using the drug" of if "there is a serious adverse reaction that can be prevented or reduced in frequency or severity…" ("Guidance for Industry," FDA, 2011, pg 11, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096)

Consistent with this FDA Guidance regarding when to add a Black Box Warning to a drug label, Levaquin Psychiatric Adverse Events are serious, may have a significant impact on quality of life, and may be prevented or reduced if physicians and patients have prominent warning through a Black Box. Levaquin Psychiatric Adverse Events, including, toxic psychoses, hallucinations, paranoia, suicidal thoughts or acts, loss of consciousness, delirium, depressed level of consciousness, amnesia, coma, and memory impairment are all serious in that the risk of experiencing these potentially life-threatening symptoms do not outweigh the benefit when Levaquin is used for FDA-

approved routine infections. These Adverse Events, therefore, meet the FDA definition of requiring a Black Box Warning.

Physicians should be adequately warned about these serious Levaquin Psychiatric Adverse Events in order to ***provide best practice medicine*** and patients should be adequately warned about these serious Levaquin Psychiatric Adverse Events in order to ***provide informed consent***. It is requested that a Black Box Warning regarding Psychiatric Adverse Events be added to the Levaquin label.

Additional Grounds for Requested Actions

A social network of individuals who report experiencing Levaquin Adverse Events report the following Psychiatric Adverse Events as indicated in the table below.

Survey Question: Describe "any psychiatric symptoms Due to Fluoroquinolone Toxicity (depression, anxiety, psychosis, etc)?"	
	N=94 % Reported
Anxiety	72%
Depression	62%
Insomnia	48%
Panic attacks	37%
Brain fog and/or cognitive impairment	33%
Depersonalization and/or derealization	29%
Thoughts of suicide	24%
Psychosis and/or hallucinations	22%
Nightmares and/or abnormal dreams	21%
Impaired memory	21%
Emotional outbursts (crying/giggling) and/or mood swings	17%
Paranoid and/or fearful	10%
Agitation	9%
Attention deficit and/or lack of concentration	9%
Sensation of impending doom	7%
Difficulty reading and/or doing math	7%
Confusion	7%
Mania and/or hyperactivity	6%
Rage and/or temper flares	5%

C. ENVIRONMENTAL IMPACT

Nothing requested in this petition will have an impact on the environment.

D. ECONOMIC IMPACT

Not applicable at this time.

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 know to the Petitioner, which are unfavorable to the Petitioner.

Respectfully yours,

Charles Bennett, M.D., Ph.D., M.P.P.
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