CITIZEN PETITION

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

Southern Network For 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)), FDCA section 505-1(a)(2)(A)((21 U.S.C. 355-1(a)(2)(a)), 21 C.F.R. 10.30, and 21 C.F.R. 208. SONAR requests that the Commissioner of the Food and Drug Administration (FDA) take the following actions: (1) add a Levaquin Black Box warning for Fluoroquinolone-Associated Disability ("FQAD"); (2) add a Levaquin Black Box warning to specifically identify psychiatric adverse events, including suicide and suicide-related adverse events; and (3) require a Risk Evaluation and Mitigation strategy (REMS) for Levaquin.

A. ACTIONS REQUESTED

This Citizen Petition requests that the FDA take the following actions:

(1) Add Fluoroquinolone-Associated Disability (FQAD) to the Levaquin Black Box Warning[1];

(2) Add Psychiatric Adverse Events to the Levaquin Black Box Warning; and

(3) Implement a New REMS for Levaquin under 21 U.S.C. § 355-1 (a)(2)(a) and 21 C.F.R. 208.1(c)(2)[2] which will require manufacturers of Levaquin develop and get approved a Levaquin REMS which would include Elements to Assure Safe Use ("ETASU") aimed at physician, patient, and pharmacy education and registration.

These actions will strengthen the quality of the Levaquin science base and decisions based upon it. Specifically, SONAR requests the following:

(1) <u>Add Fluoroquinolone-Associated Disability (FQAD) to the Levaquin Black Box Warning</u>

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

[1] The current FDA approved label and supporting materials is included as Attachment 1 to this petition.

[2] "The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product." 21 C.F.R. 208.1(c)(2).

Fluoroquinolones, including LEVAQUIN®, have been associated with disabling and potentially irreversible serious adverse events, including a constellation of disabling symptoms known as Fluoroquinolone-Associated Disability (FQAD) which may result in a substantial disruption of a person's ability to conduct normal life functions; which may be permanent; and which may affect multiple body systems, including musculoskeletal, neuropsychiatric, peripheral nervous system, vision, hearing, skin, and cardiovascular.

(2) Add Psychiatric Adverse Events to the Levaquin 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:

Fluoroquinolones, including LEVAQUIN®, have been associated with disabling and potentially irreversible serious adverse events, including psychiatric adverse reactions, which include suicide and suicide-related adverse effects.

(3) Implement a new REMS for Levaquin

It is requested that any physician that wants to prescribe Levaquin must receive specialized education and register with the FDA. *See* 21 U.S.C. 355-1(f)(3). Specifically, the REMS should include requiring healthcare providers who prescribe the drug to have particular training or experience as per 21 U.S.C. 355-1(f)(3)(A) and for providers and pharmacies to be certified under 21 U.S.C. 355-1(f)(3)(D). Physicians should be specifically educated on the risks, symptoms, and nature of FQAD. Additionally, patients using the drug should be enrolled in registry under 21 U.S.C. 355-1(f)(3)(F). Finally, the REM should include prescribing pharmacy registration.

B. STATEMENT OF GROUNDS FOR REQUESTED ACTIONS

Background

The "ACTIONS REQUESTED" are based on widely accepted science detailing the harmful and irreversible adverse effects associated with Levaquin, including FQAD and serious psychiatric adverse events. The FDA and other regulatory bodies have already relied on this science to require the following Levaquin label changes, as described by the FDA:

- "The FDA first added a Boxed Warning to fluoroquinolones in July 2008 for the increased risk of tendinitis and tendon rupture.
- In February 2011, the risk of worsening symptoms for those with myasthenia gravis was added to the Boxed Warning.
- In August 2013, the agency required updates to the labeling to describe the potential for irreversible peripheral neuropathy (serious nerve damage).

- In 2016, the FDA enhanced warnings about the association of fluoroquinolones with disabling and potentially permanent side effects involving tendons, muscles, joints, nerves and the central nervous system. Because the risk of these serious side effects generally outweighs the benefits for patients with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections, the FDA determined that fluoroquinolones should be reserved for use in patients with these conditions who have no alternative treatment options." https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics-risks-mental-health-and-low-blood-sugar-adverse

(1) Grounds for the Addition of Fluoroquinolone-Associated Disability (FQAD) to the Levaquin Black Box Warning

At the FDA Joint Meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee meeting November 5, 2015, Debra Boxwell, PharmD, from the FDA Division of Pharmacovigilance II Office of Surveillance and Epidemiology presented, "Fluoroquinolone-Associated Disability" (FQAD) Cases in Patients Being Treated for Uncomplicated Sinusitis, Bronchitis, and/or Urinary Tract Infection."

In this presentation, Dr. Boxwell defined Fluoroquinolone-Associated Disability (FQAD). Dr. Boxwell described FQAD as a "constellation of disabling symptoms" which results in "a substantial disruption of a person's ability to conduct normal life functions" and includes adverse events which "last 30 days or longer after stopping the fluoroquinolone." Dr. Boxwell further defined FQAD as including adverse events from two or more of the following body systems: musculoskeletal, neuropsychiatric, peripheral nervous system, senses (vision, hearing, etc.), skin, and cardiovascular."

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, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatorylnformation/Guidances/ucm075096)

Consistent with this FDA Guidance regarding when to add a Black Box Warning to a drug label, FQAD clearly meets the FDA requirement that the adverse reaction—or in this case the "constellation of disabling symptoms"—are so serious that the FDA has included the word "Disabling" in its name. Furthermore, by the FDA's definition of FQAD, this constellation of symptoms may continue well past the discontinuation of taking the medication and may disrupt "a person's ability to conduct normal life functions."

FQAD clearly meets the FDA's definition of requiring a Black Box warning.

It is requested that the FDA take action to specifically include "FQAD," and the FDA-defined "constellation of disabling symptoms," within the Levaquin Black Box warning.

In further support of this requested action, the detailed chart and map below indicated that since FQAD was identified by Dr. Boxwell at the November 5, 2015 meeting, FQAD cases have been, and continue to be, reported nationwide. *See* Floxed Map and Summary (Attachment 2).

The attached Map and Summary details these events in two ways. First, it maps the results of a one-day outreach program conducted by individuals in the Floxed community to identify patients that have experienced FQAD since the 2016 Levaquin and other FQ label warnings changes. A second map and corresponding spreadsheet lists and maps lawsuits filed by patients suffering from FQAD after taking an FQ after 2015 when the FDA defined FQAD. Importantly, both maps are under-inclusive, given the low reporting rate associated with adverse effects from FQs.

(2) Grounds for the Addition of Psychiatric Adverse Events to the Levaquin Black Box Warning

July 10, 2018, Janet Woodcock, M.D., FDA Director of Center for Drug Evaluation and Research, wrote in a letter to Charles Bennett, M.D. that "because the boxed warning in the labeling for fluoroquinolones, including Levofloxacin, already refers to subsection *Central Nervous System Effects*, for which we are requiring the subcategory Psychiatric adverse reactions, it is unnecessary at this time to add the psychiatric adverse reactions directly to the boxed warning."

Most physicians and patients do not know that Psychiatric adverse reactions are part of *Central Nervous System Effects*. Most physicians and patients do not expect Psychiatric adverse reactions to be part of *Central Nervous System Effects*.

Therefore, since the FDA has already stated that, by definition, Psychiatric adverse reactions are currently already included in the Black Box warning, it is requested that the FDA merely clarify this and specifically identify and add Psychiatric adverse events to the Levaquin Black Box warning.

(3) Grounds for the Implementation of a New REMS for Levaquin

FDA's Guidance for REMS requires the FDA is to consider the following six statutory factors in its analysis:

1. *The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;*

2. *The expected benefit of the drug with respect to the disease or condition;*

3. *The seriousness of the disease or condition that is to be treated with the drug;*

4. *Whether the drug is a new molecular entity;*

5. *The expected or actual duration of treatment with the drug; and*

6. *The estimated size of the population likely to use the drug.*

See April 2019 "Guidance for Industry REMS: FDA's Application of Statutory Factors In Determining When a REMS Is Necessary" ("Guidance").

The following documents the grounds for the request to implement a new REMS for Levaquin:

1. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

a. The seriousness of any known or potential adverse events that may be related to the drug:

Levaquin FQAD and Psychiatric Adverse Events are serious, have a significant impact on quality of life, and may only be prevented or reduced if physicians and patients are properly educated and aware of the risk benefit calculus through a REMS.

Levaquin Fluoroquinolone-Associated Disability (FQAD), a "constellation of disabling symptoms" which results in "a substantial disruption of a person's ability to conduct normal life functions," includes adverse events which "last 30 days or longer after stopping the fluoroquinolone," and including adverse events from two or more of the following body systems: musculoskeletal, neuropsychiatric, peripheral nervous system, senses (vision, hearing, etc.), skin, and cardiovascular," clearly do not outweigh the benefit when Levaquin is used for many FDA-approved purposes.

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 many FDA-approved purposes.

b. The background incidence of such events in the population likely to use the drug:

From December 1996 to May 2016, the FDA Adverse Events Reporting System (FAERS) received:

- **28,079** Levaquin adverse event **individual reports**,
- identifying **110,292** Levaquin **adverse events**, and
- identifying **1,765** Levaquin **deaths**

It is broadly assumed that only 1% to 10% of actual adverse events are reported to the FDA.

Because Levaquin lacked adequate adverse events warnings for a significant period of time during the period of December 1996 to May 2016, as evidenced by the updated Levaquin label

safety warnings in recent years, it is assumed that only 1% of Levaquin adverse events have been reported to the FDA.

Thus, from December 1996 to May 2016, it is estimated:

- The actual number of Levaquin adverse events **individual reports** is estimated to be **2,807,900**.
- The actual number of Levaquin **adverse events** is estimated to be **11,029,200**.
- The actual number of Levaquin **deaths** is estimated to be **176,500**.

When the above data is adjusted to include Levaquin individuals reports, adverse events, and deaths for the past three years from May 2016 to May 2019, it is assumed that from December 1996 to May 2019:

- The actual number of Levaquin adverse events **individual reports** is estimated to be **3,239,885**.
- The actual number of Levaquin **adverse events** is estimated to be **12,726,000**.
- The actual number of Levaquin **deaths** is estimated to be **203,654**.

The FDA's own FAERS data documents the extensive adverse event and death risks associated with Levaquin.

2. The expected benefit of the drug with respect to the disease or condition

While Levaquin is documented to treat complicated and uncomplicated infections, there are other alternative antibiotics which are not associated with FQAD or disabling and potentially irreversible serious psychiatric adverse events, including suicide and suicide-associated events.

3. The seriousness of the disease or condition that is to be treated with the drug

Levaquin is approved by the FDA to treat both complicated and uncomplicated infections.

4. Whether the drug is a new molecular entity

Levaquin is not a new molecular entity.

5. The expected or actual duration of treatment with the drug

The duration of treatment with Levaquin varies and is identified by the FDA on the Levaquin label. Levaquin's disabling and potentially irreversible adverse events, including FQAD and psychiatric adverse events, including suicide and suicide-associated events may be, as stated by the FDA, "irreversible," thus lasting a life-time after taking Levaquin has been discontinued.

6. The estimated size of the population likely to use the drug

In 2018, over 7,000,000 prescriptions were written for Levaquin and its generic equivalents each year[3].

Additionally, the FDA Guidance on when to offer a REMS includes other factors to consider, including (1) the reliability of scientific evidence of the adverse effect, (2) whether the adverse effect is irreversible, (3) the frequency, (4) the ability to avoid the risk of occurrence through mitigating factors, and (5) whether information about the risk is already well-spread.

(1) Reliability of Levaquin Research

FQAD and other adverse effects of Levaquin are well established by years of research. The research has already been relied on extensively by the FDA in the past to require label changes and the black box warnings, as outline above[4].

(2) Levaquin Adverse Events May Be Irreversible

As indicated above, the current Levaquin Black Box warning describes that Levaquin is "associated with disabling and potentially irreversible serious adverse reactions…."

Importantly, there is NO treatment for FQAD.

(3) Frequency and Seriousness of Levaquin Adverse Events

As described above, when the FDA FAERS data is adjusted for Levaquin individuals reports, adverse events, and deaths, the following are Levaquin estimates from December 1996 to May 2019:

- The actual number of Levaquin adverse events **individual reports** is estimated to be **3,239,885**
- The actual number of Levaquin **adverse events** is estimated to be **12,726,000**
- The actual number of Levaquin **deaths** is estimated to be **203,654**

The FDA's own FAERS data documents the extensive adverse event and death risks associated with Levaquin.

Regarding the seriousness of Levaquin adverse events, again, as indicated above, the current Levaquin Black Box warning describes that Levaquin is "associated with disabling and potentially irreversible serious adverse reactions…."

Again, and importantly, there is NO treatment for FQAD.

[3] Estimate based on data was obtained from IMS Health.

[4] As recently as July of 2018 the FDA issued a warning about the mental health side effects of FQs. *See* FDA July 10, 2018 Announcement (Attachment 3)

(4) Ability to Avoid Levaquin's Risks

Currently there is no way to administer Levaquin in a manner that would reduce the risk of FQAD, serious psychiatric adverse events, including suicide and suicide-related events, or other disabling and potentially irreversible serious adverse events.

Moreover, apart from patients that have previously experienced a harmful Levaquin side effect, there are currently no additional means of identifying patients who may be at increased risk.

Indeed, improved Levaquin Black Box warnings and the addition of a Levaquin REM represent the only ways to reduce risk.

(5) Current Availability of Levaquin Risk Information

The current labeling regime is incomplete, FQAD has not been included anywhere on the labelling and importantly, is not included in the Levaquin Black Box, despite the fact that the FDA identified this constellation of disabling symptoms as far back as 2013.

Levaquin REMS Request Summary

In sum, the all-important first factor identified in the FDA REMS Guidance to determine if a REMS is required is:

> "A drug that is **associated with a risk of a serious adverse event that is irreversible**, such as one that causes a permanent disability or persistent incapacity, may be particularly likely to have a favorable benefit-risk profile only in the presence of a REMS that helps minimize drug exposure and the associated occurrence of the adverse event.") Guidance p. 6.

It is unequivocal that Levaquin meets this requirement in that the current Levaquin Black Box states that:

> **Fluoroquinolones, including LEVAQUIN®, have been "associated with disabling and potentially irreversible serious adverse reactions…"**

Since the FDA has already clearly stated in the Levaquin Black Box that Levaquin is **"associated with disabling and potentially irreversible serious adverse reactions…"** this indicates a Levaquin REMS is necessary and appropriate.

Moreover, the FDA REMS Guidance states that "[s]uch REMS are designed to ensure that patients are fully informed of the serious risk before beginning therapy and may involve patient acknowledgment forms or other methods of documenting that such patient-provider discussions have taken place. This kind of REMS is particularly important for drugs with limited available methods of preventing the actual occurrence of drug-associated adverse events."

As indicated above, there is NO method for preventing the actual occurrence of Levaquin-associated adverse events. This further indicates that a Levaquin REMS is necessary and appropriate.

In sum, FQAD and serious psychiatric adverse events, including suicide and suicide-related adverse events are frequent, widespread, may be irreversible, and cannot be prevented.

Therefore, Levaquin should be subject to a REMS that includes "prescriber decisions about treatment with the drug. Such REMS are designed to ensure that patients are fully informed of the serious risk before beginning therapy and may involve patient acknowledgment forms or other methods of documenting that such patient-provider discussions have taken place." *See* Guidance.

D. ENVIRONMENTAL IMPACT

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

E. ECONOMIC IMPACT

Not applicable at this time.

F. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: June 17, 2019. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: N/A. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.', with the date on which such information first became known to such party and the names of such persons or organizations inserted in the first and second blank space, respectively.

Respectfully Yours,

Charles Bennett, M.D., Ph.D., M.P.P.
Center for Medication Safety and Efficacy
Southern Network on Adverse Reactions (SONAR),
South Carolina College of Pharmacy/USC Campus
715 Sumter Street, Suite 311-L
Columbia SC 29208
803-777 -2289-office
803-777 -2820-fax

.