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Southern Network on Adverse Reactions (SONAR)
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JUL 10 2018

Re: Docket No. FDA-2014-P-1611

Dear Dr. Bennett:

This letter responds to the citizen petition (Petition) submitted to the Food and Drug Administration (FDA or the Agency) by the Southern Network on Adverse Reactions (SONAR) and received on September 11, 2014. The Petition requests that FDA require changes in the professional labeling of Levaquin (levofloxacin) "in order to specify a more accurate benefit/risk profile for this antibiotic" (Petition at 1).[1]

Specifically, SONAR requests that:

1. Additional psychiatric adverse events[2] (feeling abnormal, loss of consciousness, disorientation, agitation, delirium, depressed level of consciousness, amnesia, coma, disturbance in attention, panic attack, memory impairment, and nervousness) be added to the labeling for levofloxacin products (Petition at 1-2);

2. FDA require a separate *Psychiatric Effects* subsection under the WARNINGS AND PRECAUTIONS section of the labeling for levofloxacin products rather than listing psychiatric adverse events under the *Central Nervous System Effects* subsection of the labeling (Petition at 2); and

3. Serious psychiatric adverse events including toxic psychoses, hallucinations, paranoia, suicidal thoughts or acts, loss of consciousness, delirium, depressed level of

[1] Although your Petition only cited the new drug application (NDA) number pertaining to the tablet form of Levaquin (levofloxacin), NDA 020634 (Petition at 1), we also considered your requests in light of NDAs 020635 and 021721 pertaining to the solution formulations of Levaquin (levofloxacin). All of the Levaquin products are currently discontinued from sale. There are numerous approved generic levofloxacin products that are currently on the market. We also considered your requests in light of systemic fluoroquinolones (i.e., ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, and delafloxacin) as a class of drugs because the current labeling of central nervous system and psychiatric adverse reactions are similar among all systemic fluoroquinolones.

[2] Although petitioner has characterized these terms as "psychiatric adverse events," FDA does not agree that all of petitioner's requested terms are considered psychiatric events. FDA has determined that the terms "loss of consciousness," "depressed level of consciousness," and "coma," are better characterized as central nervous system disorders. The term "feeling abnormal" is a general term that is not considered either a central nervous system disorder or a psychiatric event.

consciousness, amnesia, coma, and, memory impairment, be added to the current boxed warning on the labeling for levofloxacin products (Petition at 2).

We have carefully reviewed the information in the Petition, as well as other relevant information. For the reasons stated below, we grant your request insofar as we are taking action to require certain changes to the labeling of levofloxacin products and other systemic fluoroquinolone antibacterial drugs to reflect new safety information. The petition is otherwise denied.

I. BACKGROUND

A. Statutory and Regulatory Framework

New drug applications (NDAs) contain, among other things, scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. NDA applicants must, among other things, describe the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions of use stated in the drug product's labeling.[3]

Certain prescription drug labeling (e.g., the prescribing information) is approved by FDA. The prescribing information is a compilation of information about the product, based on the Agency's review of the NDA submitted by the applicant. It contains a summary of the essential scientific information needed for the safe and effective use of the drug.[4] Labeling for prescription drug products is generally governed by 21 CFR 201.50, *et seq.*, with specific requirements for content and format set forth in 21 CFR 201.57. Under section 201.57, drug product labeling must describe clinically significant adverse reactions,[5] other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these occur (21 CFR 201.57(c)(6)(i)). Labeling for prescription drugs must be revised to include warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug (id.).

The WARNINGS AND PRECAUTIONS section of labeling must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.[6] Specifically, § 201.57(c)(6) requires that the WARNINGS AND PRECAUTIONS section of labeling:

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[3] 21 CFR 314.50(d)(5)(viii).

[4] 21 CFR 201.57.

[5] Section 201.57(c)(7) defines "adverse reaction" as "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." *See also* FDA guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, October 2011 (Warnings Guidance), at 3-5. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] § 201.57(c)(6).

> . . . describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). . . . [T]he labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established.

In addition, FDA clarified in the Warnings Guidance[7] that:

> [t]he WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.

FDA may require that "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury . . . be presented in a box" on a drug product's labeling.[8] Specifically, § 201.57(c)(1) states:

> Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

Furthermore, in the Warnings Guidance, FDA explained that a boxed warning is ordinarily used to highlight one of the following situations:[9]

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug; or

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[7] Warnings Guidance at 3.

[8] § 201.57(c)(1).

[9] Warnings Guidance at 11.

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug . . .; or

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted . . . .

The Warnings Guidance also elaborates on certain other circumstances in which a boxed warning can also be appropriate, including to highlight warning information that is especially important to the prescriber.

After an approved drug enters the market, FDA may require the inclusion of new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions, in product labeling. Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require and, if necessary, order labeling changes if FDA becomes aware of new safety information that FDA determines should be included in the labeling of the drug.

B. Levofloxacin

Levaquin is approved under NDAs 020634, 020635, and 021721, all currently held by Janssen Pharmaceuticals, Inc. Levaquin (levofloxacin) is a synthetic, broad-spectrum fluoroquinolone antibacterial drug for oral and intravenous administration. In addition, there are many FDA-approved generic levofloxacin products for systemic use. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. Levofloxacin is indicated in adults (≥18 years of age) with infections caused by designated susceptible bacteria listed in section 1 of the labeling for the following conditions: nosocomial pneumonia; community-acquired pneumonia; acute bacterial sinusitis; acute bacterial exacerbation of chronic bronchitis; complicated skin and skin structure infections; uncomplicated skin and skin structure infections (mild to moderate); chronic bacterial prostatitis; complicated urinary tract infections; acute pyelonephritis; uncomplicated urinary tract infections (mild to moderate); and inhalational anthrax (post-exposure). Levofloxacin is also indicated for treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis* and prophylaxis for plague in adults and pediatric patients, 6 months of age and older. [10]

The labeling for levofloxacin products contains the following boxed warning:

[10] See current labeling for Levaquin (NDA 020634, 020635, and 021721), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020634s068,020635s074,021721s035lbl.pdf.

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

- Fluoroquinolones, including BRAND NAME, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including:
  - o Tendinitis and tendon rupture
  - o Peripheral neuropathy
  - o Central nervous system effects

  Discontinue BRAND NAME immediately and avoid the use of fluoroquinolones, including BRAND NAME, in patients who experience any of these serious adverse reactions
- Fluoroquinolones, including BRAND NAME, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid BRAND NAME in patients with known history of myasthenia gravis.
- Because fluoroquinolones, including BRAND NAME, have been associated with serious adverse reactions, reserve BRAND NAME for use in patients who have no alternative treatment options for the following indications:
  - o Uncomplicated urinary tract infection
  - o Acute bacterial exacerbation of chronic bronchitis
  - o Acute bacterial sinusitis

Other serious risks associated with fluoroquinolones are described in the labeling, such as cardiac, dermatologic, and hypersensitivity reactions. The labeling also includes warnings about the risk of peripheral neuropathy and central nervous system effects. The labeling states under the *Central Nervous System Effects* subsection:

> Fluoroquinolones, including BRAND NAME, have been associated with an increased risk of central nervous system (CNS) effects, including convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri). Fluoroquinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, and insomnia. Suicidal thoughts, and attempted or completed suicide may also occur, especially in patients with a medical history of depression or an underlying risk factor for depression. These reactions may occur following the first dose. If these reactions occur in patients receiving BRAND NAME, discontinue BRAND NAME and institute appropriate measures. As with other fluoroquinolones, BRAND NAME should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction).

In addition, the INDICATIONS AND USAGE section contains limitation-of-use statements communicating that because fluoroquinolones have been associated with serious adverse reactions, they should be reserved for patients who do not have other available treatment options for the following indications: acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections. A Medication Guide is required to be given to the patient with each fluoroquinolone prescription, conveying important information patients should have about serious side effects associated with these medicines.

II. DISCUSSION

In your Petition, you request that FDA require changes in the labeling for levofloxacin products to reflect new safety information.[11] Specifically, you request that (1) additional "psychiatric" adverse reactions be added to the WARNINGS AND PRECAUTIONS section of the labeling for levofloxacin products (Petition at 1-2), (2) a separate subsection titled *Psychiatric Effects* be included in the WARNINGS AND PRECAUTIONS section of labeling (Petition at 2), and (3) a boxed warning be added to the labeling for levofloxacin products regarding psychiatric adverse reactions (Petition at 2).

For the reasons explained further below, we agree that changes are needed in the professional labeling for levofloxacin products to reflect new safety information. Therefore, today we issued letters to the holders of approved applications for levofloxacin and other systemic fluoroquinolones notifying them that they are required to make revisions to their labeling. In sum, these revisions include:

- The WARNINGS AND PRECAUTIONS section of labeling for systemic fluoroquinolones, including Levaquin, will include the terms:
    - agitation
    - delirium
    - disturbances in attention
    - memory impairment
    - disorientation
    - nervousness

- The subsection *Central Nervous System Effects* will be broken into two subcategories, Psychiatric adverse reactions and Central nervous system adverse reactions.

For the reasons set forth below, your requests are granted insofar as we are requiring that certain changes be made to the Warnings and Precautions section of the labeling for levofloxacin products and other systemic fluoroquinolone antibacterial drugs. Otherwise, your petition is denied.

A. Additional Psychiatric Adverse Reactions in the WARNINGS AND PRECAUTIONS Section

We agree that additional psychiatric adverse reactions should be included in the WARNINGS AND PRECAUTIONS section of labeling for systemic fluoroquinolones, including levofloxacin products. However, we do not agree that all of your proposed adverse reactions should be included in the WARNINGS AND PRECAUTIONS section of labeling for systemic fluoroquinolones, for the reasons set forth below.

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[11] As indicated above in the first footnote, although your Petition only cited the NDA number pertaining to the tablet form of Levaquin (levofloxacin), NDA 026034 (Petition at 1), we also considered your requests in light of NDAs 020635 and 021721 pertaining to the solution formulations of Levaquin (levofloxacin) and to other systemic fluoroquinolones, including ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, and delafloxacin.

You have identified the following twelve additional adverse reactions that you state should be added to the WARNINGS AND PRECAUTIONS section of Levaquin's labeling: feeling abnormal, loss of consciousness, disorientation, agitation, delirium, depressed level of consciousness, amnesia, coma, disturbance in attention, panic attack, memory impairment, and nervousness (Petition at 1-2). Your Petition states that these symptoms are "serious Psychiatric Adverse Events, but are not listed on the Levaquin labeling under 'Warnings and Precautions'" (Petition at 3). In support of your position, you reference data from the FDA Adverse Event Reporting System (FAERS) using a variety of adverse event terms from the period November 1997 to June 2012 (Petition at 3). You also refer to the results of a social network survey of individuals who reported experiencing psychiatric events (Petition at 5). We question the reliability of the results of the social network survey because there were no results of qualitative research to support the development of the survey questions regarding psychiatric symptoms. Additionally, the survey did not identify individuals with comorbidities or established psychiatric diagnoses before taking fluoroquinolone.

We have performed our own review of FAERS reports[12] on levofloxacin and other marketed systemic fluoroquinolones in the U.S., as well as a literature search for any articles having a primary focus on levofloxacin and adverse events associated with each of the twelve proposed terms.

For the reasons set forth below, we agree that some, but not all, of your proposed adverse reactions for the psychiatric section should be included in the WARNINGS AND PRECAUTIONS section of labeling for systemic fluoroquinolones, including levofloxacin.

1. Terms to be Added to Labeling for Systemic Fluoroquinolones

We agree with you that the terms, "agitation," "delirium," "disturbance in attention," "memory impairment," "disorientation," and "nervousness" should be included in the WARNINGS AND PRECAUTIONS section of the labeling for all systemic fluoroquinolones, including levofloxacin.

The term "agitation" currently appears in the WARNINGS AND PRECAUTIONS sections of the ciprofloxacin, moxifloxacin, ofloxacin, and delafloxacin labeling and in the ADVERSE REACTIONS section of the labeling for levofloxacin products. In our review, we found reasonable evidence of a causal association between agitation and levofloxacin and gemifloxacin use. Based on our review and for the purposes of consistent class labeling, we agree that "agitation" should be included in the WARNINGS AND PRECAUTIONS section of the labeling for all systemic fluoroquinolones, including levofloxacin.

With respect to the term, "delirium," in many cases the onset of delirium occurred after the patient showed improvement in the infectious disease process, and the adverse reaction of

[12] The FAERS database was searched using the adverse event terms you request be added to the WARNINGS AND PRECAUTIONS section of labeling and the product term (e.g., levofloxacin sodium) for the time period beginning with the date of approval of the drug and ending with the date that the search was conducted.

delirium seemed to be attributable to the fluoroquinolone antibacterial drug and not to the infection. The onset of delirium was closely associated with the administration of levofloxacin therapy, and most patients reported rapid recovery after levofloxacin was discontinued. A literature search identified a total of seven case reports of delirium associated with levofloxacin administration, and five of these cases were reported to MedWatch and were included in the FAERS case series. Based on our review of levofloxacin and cases of delirium reported to FAERS for the other fluoroquinolones, we agree that it is appropriate to include "delirium" in the WARNINGS AND PRECAUTIONS section of labeling for systemic fluoroquinolone medications.[13]

Regarding the term, "disturbances in attention," although some cases contained colloquial wording such as "brain fog," other cases more clearly described a lack of attention or lack of an ability to concentrate on performing tasks. Based on our FAERS review of levofloxacin and cases of disturbances in attention reported to FAERS for the other fluoroquinolones, we found reasonable evidence of a causal association between disturbance in attention and systemic fluoroquinolone use, including levofloxacin. Moreover, 61 percent of patients who reported a disturbance in attention after receiving levofloxacin reported it was disabling and potentially irreversible. In some of the reports, the patient lost employment attributed to his or her lack of concentration and disturbances in attention. We agree that the psychiatric adverse reaction, "disturbances in attention," should be included in the WARNINGS AND PRECAUTIONS section of labeling because of the potential significant impact of systemic fluoroquinolone use on patients.

For "amnesia" and "memory impairment," which were evaluated together, we found reasonable evidence of a causal association between fluoroquinolone use, including levofloxacin, and memory impairment, based on the FAERS review of levofloxacin and cases of memory impairment reported to FAERS for the other fluoroquinolones.[14] Additionally, 78 percent of patients who developed memory impairment after receiving levofloxacin reported it to be disabling and potentially irreversible. Based on these data and because psychiatric adverse reactions can affect a patient's quality of life, we agree that the term "memory impairment" should be included in the WARNINGS AND PRECAUTIONS section of labeling. We decline, however, to require that the term "amnesia" be added to the labeling because the FAERS cases that were coded as "amnesia" more accurately described memory impairment.

From a clinical perspective, the term "disorientation" is similar in meaning to the term "confusion," which already appears in the labeling subsections headed *Central Nervous System Effects* and *Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy* for all fluoroquinolones, including levofloxacin. However, the term "disorientation" appears in the ADVERSE REACTIONS section of the labeling for moxifloxacin and ofloxacin, and we found reasonable evidence of a causal association between "disorientation" and levofloxacin, ciprofloxacin, and gemifloxacin. Accordingly, we have determined that it is appropriate for the term "disorientation" to be

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[13] "Delirium" is currently in the ciprofloxacin labeling and can be found in the ADVERSE REACTIONS section.

[14] The terms "amnesia" and "memory impairment" were evaluated together because they are redundant, and "memory impairment" is a broad adverse event preferred term that captures related terms including "amnesia."

included in the WARNINGS AND PRECAUTIONS section of labeling for all the systemic fluoroquinolones, including levofloxacin.

Finally, regarding the term "nervousness," our review of the FAERS data found reasonable evidence of a causal association between levofloxacin use and reports of "nervousness." The labeling for ciprofloxacin, gemifloxacin, moxifloxacin, ofloxacin, and delafloxacin contains this term in the WARNINGS AND PRECAUTIONS section. Accordingly, we have determined that it is appropriate for the term "nervousness" to be included in the WARNINGS AND PRECAUTIONS section of labeling for all the systemic fluoroquinolones, including levofloxacin.

2. *Nonspecific Term*

You request that the term, "feeling abnormal," be added to the labeling for levofloxacin products. In the FAERS cases coded as "feeling abnormal," patients typically did not report "feeling abnormal" but rather non-specific and more vague experiences that covered a wide range of adverse events consistent with not feeling well. This term is nonspecific and does not adequately describe an adverse reaction in sufficient detail such that it is informative; a precise medical definition for this term could not be found. Although this term does not fall under the nervous system or psychiatric body systems, other neuropsychiatric adverse event terms in the labeling are more specific and informative. Accordingly, we will not require changes to product labeling to include the term "feeling abnormal."

3. *Lack of Reasonable Evidence for a Causal Association Between Other Adverse Events and Systemic Fluoroquinolone Use*

At this time, we conclude that, for some of the terms you would like added to the labeling for levofloxacin products, there is no reasonable evidence demonstrating a causal association between the adverse event and the drug.

The terms "depressed level of consciousness" and "loss of consciousness" were considered together because the terms are clinically similar and only differ in the degree of impairment. However, there is no reasonable evidence generally demonstrating a causal relationship between "depressed level of consciousness" or "loss of consciousness" and levofloxacin use. These conditions or events are generally symptomatic of a serious medical event, which may or may not be related to levofloxacin use. "Loss of consciousness" is already labeled as an adverse reaction associated with hypersensitivity reactions and prolongation of the QT interval for levofloxacin and the other fluoroquinolones.[15] We believe that the term "loss of consciousness" is appropriately listed as an adverse reaction in these sections of the labeling for fluoroquinolones, and we decline to treat this term as a psychiatric adverse reaction in the WARNINGS AND PRECAUTIONS section.

[15] See Levaquin labeling, *Hypersensitivity Reactions* under WARNINGS AND PRECAUTIONS and "Prolongation of the QT Interval" under PATIENT COUNSELING INFORMATION.

With respect to "coma," nearly all cases with levofloxacin were a result of a reported serious medical event, including hypoglycemia, and there was no evidence of levofloxacin being the direct cause of coma; in the remaining cases, there was insufficient information reported to identify a causal association with levofloxacin. However, there was a small cluster of cases in which coma appeared to be related to profound hypoglycemia, and hypoglycemia is already listed in subsection *Blood Glucose Disturbances* under the WARNINGS AND PRECAUTIONS section of the labeling for levofloxacin products. Because of the serious safety concerns associated with use of systemic fluoroquinolones and hypoglycemic coma, we are seeking changes to the *Blood Glucose Disturbances* subsection of the labeling for all systemic fluoroquinolones to explicitly reflect the potential risk of coma with hypoglycemia. We are not seeking changes to the *Central Nervous System Effects* section of the labeling regarding coma.

We considered whether the term "panic attack" should be added to labeling. The FAERS reports did not include adequate clinical information to confirm that the episodes were panic attacks. Given the limited clinical descriptions in reports, we were unable to conclude that reasonable evidence of causal association has been established. Moreover, we note the broader term "anxiety" is already included as an adverse event in the *Central Nervous System Effects* and the *Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects* sections of labeling for all fluoroquinolones, including levofloxacin. At this time, we believe there is insufficient evidence to require the term "panic attack" be added to the labeling.

In sum, your request is granted to the extent that we are requiring inclusion of the following terms in the WARNINGS AND PRECAUTIONS section of labeling for all systemic fluoroquinolones, including levofloxacin: "agitation," "delirium," "disturbances in attention," "memory impairment," "disorientation," and "nervousness," in the *Central Nervous System Effects* subsection. In addition, we are requiring "hypoglycemic coma" be added to the *Blood Glucose Disturbances* subsection in the WARNINGS AND PRECAUTIONS section of the labeling for these products. Your request is denied to the extent that we decline to include "coma" under the *Central Nervous System Effects* subsection of the WARNINGS AND PRECAUTIONS section, or require changes to the labeling for all systemic fluoroquinolones, including levofloxacin, to include the following terms in the WARNINGS AND PRECAUTIONS section: "feeling abnormal," "depressed level of consciousness," "loss of consciousness," "panic attack," and "amnesia."

B. Separate Heading for Psychiatric Adverse Reactions Under the WARNINGS AND PRECAUTIONS Section

You request that "a specific 'Psychiatric Effects' heading be added under the 'Warnings and Precautions' section of the Levaquin labeling rather than listing Levaquin Psychiatric Adverse Events under the 'Central Nervous System Effects' heading, as is currently done" (Petition at 2). We generally agree with the concept of separating psychiatric adverse reactions from other central nervous system effects for the sake of clarity. Currently, the *Central Nervous System Effects* subsection describes both psychiatric adverse reactions (e.g., toxic psychosis) and other central nervous system adverse reactions (e.g., convulsions) without any clear delineation between the two types of adverse reactions. Rather than create a new subsection for psychiatric

adverse reactions, we will require two subcategories, Psychiatric adverse reactions and Central nervous system adverse reactions, under subsection *Central Nervous System Effects*.

You further request that a subsection for psychiatric adverse reactions have the following language:

> 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.

(Petition at 2). We do not agree with your proposed wording for this subsection of the labeling. As stated above in section II.A of this letter, we will not update the labeling for fluoroquinolones to include the following psychiatric adverse events: "feeling abnormal," "depressed level of consciousness," "loss of consciousness," "coma," "panic attack," and "amnesia." Accordingly, these terms will not be required in the labeling. FDA is requiring changes to the labeling for systemic fluoroquinolones, including levofloxacin, using the newly formed subcategories, as follows:

> **5.4 Central Nervous System Effects**
>
> Psychiatric adverse reactions
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> Fluoroquinolones, including BRAND NAME, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychoses, hallucinations, or paranoia; depression, or suicidal thoughts; anxiety, agitation, restlessness, or nervousness; confusion, delirium, disorientation, or disturbances in attention; lightheadedness; insomnia or nightmares; memory impairment. Attempted or completed suicide have been reported, especially in patients with a medical history of depression, or an underlying risk factor for depression. These reactions may occur following the first dose. If these reactions occur in patients receiving BRAND NAME, discontinue BRAND NAME and institute appropriate measures.
>
> Central nervous system adverse reactions
>
> Fluoroquinolones, including BRAND NAME, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (including pseudotumor cerebri), tremors, and lightheadedness. As with other fluoroquinolones, BRAND NAME should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). If these reactions occur in patients receiving BRAND NAME, discontinue BRAND NAME and institute appropriate measures. [*see Adverse Reactions (6); Drug Interactions (7.4, 7.5); Patient Counseling Information (17.3)]*.

Accordingly, your request is granted to the extent that we have separated psychiatric adverse reactions from other central nervous system adverse reactions in the labeling. However, psychiatric adverse reactions will be listed as a separate subcategory under the subsection

Central Nervous System Effects. Your request is denied to the extent that psychiatric adverse reactions will not be listed under a separate subsection from *Central Nervous System Effects* in the labeling for systemic fluoroquinolones. Your request for specific language for this subsection is also denied to the extent that we have denied including additional adverse reactions, as explained above in section II.A.

C. Psychiatric Adverse Reactions as Part of the Boxed Warning

You request that the Agency require psychiatric adverse reactions be added to the boxed warning (Petition at 2). 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. Accordingly, this request is denied.

III. CONCLUSION

For the reasons explained above, your Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research