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Southern Network on Adverse Reactions (SONAR)
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715 Sumter Street, Suite 311-L
Columbia, SC 29208

August 28, 2020

Re: Docket No. FDA-2019-P-2998

Dear Dr. Bennett:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA or Agency) by the Southern Network on Adverse Reactions (SONAR) and received on June 20, 2019 (Petition). The Petition requests that FDA require changes in the professional labeling of Levaquin (levofloxacin) (new drug application (NDA) 020634) and require a risk evaluation and mitigation strategy (REMS) for Levaquin.[1]

Specifically, SONAR requests that FDA take the following actions:

(1) Add Fluoroquinolone-Associated Disability (FQAD)[2] to the Levaquin Black Box Warning

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

(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) 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

(Petition at 1).

We have carefully reviewed the information in the Petition, as well as other relevant information. For the reasons stated below, we deny your Petition.

[1] Although your Petition only cited the 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 the applicability of your requested labeling changes to systemic fluoroquinolones (i.e., ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, ofloxacin, and delafloxacin) as a class of drugs.

[2] The Petition refers to "FQAD". However, this term is not accepted medical terminology and is not used in clinical practice. We interpret the Petition's use of "FQAD" to refer to the disabling and potentially irreversible serious adverse reactions in different body systems that can occur together in the same patient with fluoroquinolone use and as described in the Boxed Warning, the WARNINGS AND PRECAUTIONS, and the PATIENT COUNSELING INFORMATION sections of the labeling. See current labeling for Levaquin (NDA 020634, 020635, and 021721), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020634s073lbl.pdf.

I. BACKGROUND

A. Statutory and Regulatory Framework

1. Labeling

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 stated in the drug product's labeling.[3]

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 § 201.57 (21 CFR 201.57). Under § 201.57, the WARNINGS AND PRECAUTIONS section of prescription drug labeling must describe clinically significant adverse reactions,[4] other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these occur (§ 201.57(c)(6)(i)). Labeling for prescription drugs "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." § 201.57(c)(6)(i).

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" within a drug product's labeling.[5] 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 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), FDA explained that a boxed warning is ordinarily used to highlight one of the following situations:

[3] 21 CFR 314.50(d)(5)(viii).
[4] 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."
[5] 21 CFR 201.57(c)(1).

- 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

- 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[6]

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, or information related to reduced effectiveness in product labeling. Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(4)) authorizes FDA to require labeling changes if FDA becomes aware of new safety information that FDA determines should be included in the labeling of the drug.

2. Risk Evaluation and Mitigation Strategy

Section 505-1(a) of the FD&C Act authorizes FDA to require applicants[7] to submit a proposed REMS when FDA has determined that a REMS is necessary to ensure that a drug's benefits outweigh its risks.[8] Generally, REMS may include a Medication Guide, a patient package insert, a communication plan, and certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose.[9] FDA may also require certain elements to assure safe use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug.[10] ETASU include medical interventions or other actions healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient such as a requirement to undergo monthly laboratory testing. ETASU may include, for example, requirements that healthcare providers who prescribe the drug have particular training or experience, that patients

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] Section 505-1 of the FD&C Act applies to any application for approval of a prescription drug submitted under section 505(b) or (j) of the FD&C Act (thus including both NDAs, including those submitted under section 505(b)(2) of the FD&C Act and abbreviated new drug applications submitted under 505(j), as well as applications submitted under section 351 of the Public Health Service Act. See section 505-1(b)(2) of the FD&C Act, referencing section 505(p)(1)(A) of the FD&C Act.

[8] Section 505-1(a) of the FD&C Act.

[9] Section 505-1(e) of the FD&C Act.

[10] Section 505-1(f)(3) of the FD&C Act.

using the drug be subject to certain monitoring, or that the drug be dispensed to patients with evidence or other documentation of safe use conditions.[11]

B. Levofloxacin

Levaquin is approved under NDAs 020634, 020635, and 021721, all currently held by Janssen Pharmaceuticals, Inc. Levaquin (levofloxacin) is a synthetic fluoroquinolone antibacterial drug for oral and intravenous administration. Additionally, FDA has approved many 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, caused by *Yersinia pestis* and prophylaxis for plague in adults and pediatric patients 6 months of age and older.[12]

Systemic fluoroquinolones have undergone multiple safety labeling changes. On July 8, 2008, FDA required makers of systemic fluoroquinolones to add a boxed warning to the labeling to include information about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones.[13] On August 15, 2013, the Agency required the labeling and Medication Guides for all systemic fluoroquinolones to better describe the serious side effect of peripheral neuropathy.[14] On July 26, 2016, FDA approved changes to the labeling for fluoroquinolone antibacterial drugs for systemic use to include in boxed warnings that these medications were associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient.[15] On July 10, 2018, FDA required safety labeling changes for systemic fluoroquinolones to strengthen the warnings about the risks of mental health side effects and serious blood sugar

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[11] Id.

[12] See current labeling for Levaquin (NDA 020634, 020635, and 021721), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020634s073lbl.pdf.

[13] FDA, "Information for Healthcare Professionals: Fluoroquinolone Antimicrobial Drugs [Ciprofloxacin (Marketed as Cipro and Generic Ciprofloxacin), Ciprofloxacin Extended-Release (Marketed as Cipro XR and Proquin XR), Gemifloxacin (Marketed as Factive), Levofloxacin (Marketed as Levaquin), Moxifloxacin (Marketed as Avelox), Norfloxacin (Marketed as Noroxin), and Ofloxacin (Marketed as Floxin)]," July 8, 2008, available at http://wayback.archive-it.org/7993/20170112032310/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126085.htm.

[14] FDA, "FDA Drug Safety Communication: FDA Requires Label Changes To Warn of Risk for Possibly Permanent Nerve Damage from Antibacterial Fluoroquinolone Drugs Taken by Mouth or by Injection," August 15, 2013, available at https://www.fda.gov/media/86575/download.

[15] FDA, "FDA Drug Safety Communication: FDA Updates Warnings for Oral and Injectable Fluoroquinolone Antibiotics Due to Disabling Side Effects," July 26, 2016, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics.

disturbances, including that low blood sugar levels could lead to coma.[16] On December 20, 2018, FDA required that labeling for fluoroquinolones be updated with information on the rare but serious risk for aortic ruptures that can lead to dangerous bleeding or even death.[17]

II. DISCUSSION

In your Petition, you request that FDA require sponsors to add FQAD and psychiatric adverse events to the boxed warning for Levaquin (Petition at 1). The Petition further requests that the Agency require a REMS for Levaquin to include an ETASU that would require: (1) physician education on the risks, symptoms, and nature of FQAD; (2) patient enrollment in a registry; and (3) registration by prescribing pharmacies (Petition at 1-2).

For the reasons set forth below, your requests are denied.

A. Fluoroquinolone-Associated Disability

The Petition states that "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" (Petition at 3). The Petition states that FQAD continues to be reported nationwide (Petition at 4). The Petition states that, as a result, "FQAD clearly meets the FDA's definition of requiring a Black Box warning" (Petition at 4). We do not agree that "FQAD" should be added to the boxed warning in the Levaquin labeling.

We continue to evaluate postmarketing safety information for Levaquin and other fluoroquinolones and have determined that no labeling changes are warranted at this time.

The current labeling for Levaquin and other systemic fluoroquinolones already addresses "disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient."[18] The labeling states that "[c]ommonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion)," and that "[t]hese reactions can occur within hours to weeks after starting LEVAQUIN."[19] The Patient Counseling Information section of the labeling also encourages prescribers to inform patients of such disabling and potentially irreversible serious adverse reactions that may occur together.[20] The boxed warning also refers to these adverse reactions.[21]

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[16] FDA, "FDA Drug Safety Communication: FDA Reinforces Safety Information About Serious Low Blood Sugar Levels and Mental Health Side Effects With Fluoroquinolone Antibiotics; Requires Label Changes," July 10, 2018, available at https://www.fda.gov/media/114192/download.

[17] FDA, "FDA Drug Safety Communication: FDA Warns About Increased Risk of Ruptures or Tears in the Aorta Blood Vessel With Fluoroquinolone Antibiotics in Certain Patients," December 20, 2018, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics.

[18] Levaquin labeling, WARNINGS AND PRECAUTIONS.

[19] Id.

[20] Levaquin labeling, PATIENT COUNSELING INFORMATION.

[21] Levaquin labeling, HIGHLIGHTS OF PRESCRIBING INFORMATION.

Moreover, the Medication Guide that describes these adverse reactions is required to be dispensed with each Levaquin prescription.

Because the current labeling for Levaquin adequately addresses disabling and potentially irreversible serious adverse reactions that can occur together, we do not agree that updates to the current boxed warning are necessary at this time.

B. Psychiatric Adverse Reactions

The Petition claims that "[m]ost physicians do not know that Psychiatric adverse reactions are part of the *Central Nervous System Effects*" and that "[m]ost physicians and patients do not expect Psychiatric adverse reactions to be part of *Central Nervous System Effects*" (Petition at 4). Accordingly, the Petition requests that FDA "[a]dd Psychiatric Adverse Events to the Levaquin Black Box warning" (Petition at 1, 4).

We do not agree that a direct reference to psychiatric adverse reactions needs to be included in the boxed warning for Levaquin. The boxed warning already includes information about Levaquin being "associated with disabling and potentially irreversible adverse reactions that have occurred together," including central nervous system effects.[22] The boxed warning further refers to section 5.4, Central Nervous System Effects, of the labeling, which separates into the subheadings Psychiatric Adverse Reactions and Central Nervous System Adverse Reactions to provide enhanced clarity. The Psychiatric Adverse Reactions subheading states:

> Fluoroquinolones, including LEVAQUIN, 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; 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 LEVAQUIN, discontinue LEVAQUIN and institute appropriate measures.[23]

In October 2018, the Agency required safety labeling changes for all fluoroquinolone labeling to include these two subheadings under section 5.4, partly in response to the citizen petition submitted by SONAR on September 11, 2014 (FDA-2014-P-1611).

We believe that the labeling for Levaquin adequately conveys potential psychiatric adverse reactions associated with Levaquin use. We have no reason to believe that patients or prescribers are confused about psychiatric adverse reactions being part of central nervous system effects.

[22] Id.

[23] Levaquin labeling, section 5.4, Central Nervous System Effects.

C. Risk Evaluation and Mitigation Strategy and Elements to Assure Safe Use

The Petition states that "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" (Petition at 5). The Petition reviews information about Levaquin in the context of the statutory factors discussed in FDA's guidance for industry *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019) (REMS Guidance) (Petition at 4-7) and stresses the disabling and potentially irreversible serious reactions that may be associated with Levaquin use as further support for requiring a REMS (Petition at 8). Accordingly, the Petition requests that Levaquin be subject to a REMS (Petition 9).

The statutory standard for FDA approval of a drug is that the drug is shown to be safe and effective for its labeled indications under its labeled conditions of use.[24] FDA's determination that a drug is safe, however, does not suggest an absence of risk. A drug is considered safe if it has an appropriate benefit-risk balance. For the majority of drugs, routine risk mitigation measures, such as providing healthcare providers with risk information through FDA-approved prescribing information, are sufficient to preserve benefits while minimizing risks.

We do not agree that a REMS is necessary to ensure that the benefits of Levaquin outweigh its risks. As explained in section I.B of this letter, the labeling for Levaquin has undergone numerous updates to inform prescribers and patients of the risks associated with Levaquin use. Moreover, the labeling stresses that because Levaquin has been associated with serious adverse reactions, it should be reserved for use in patients who have no alternative treatment options for uncomplicated urinary tract infections, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis. Even with the serious risks associated with Levaquin, it may be an appropriate choice for a patient, depending on factors including allergy history, antimicrobial susceptibility, drug interactions, and side effects. Such risks are adequately communicated in Levaquin's approved labeling.

Citing the REMS Guidance, the Petition states that "[s]ince 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" (emphasis in original) (Petition at 8). However, the statute does not require that an association with a serious adverse event that is potentially irreversible means a drug must have a REMS, nor does the REMS Guidance say that it necessarily should. FDA makes decisions about requiring a REMS as part of a benefit-risk determination for a drug after conducting an evaluation that includes integrated consideration of each of the factors outlined in section 505-1(a)(1) of the FD&C Act.[25] The relative importance or weight of each factor is a case-specific inquiry.

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[24] See section 505(d) of the FD&C Act. See also REMS Guidance.

[25] Section 505-1(a)(1) of the FD&C Act requires FDA to consider the following six factors in making a decision about whether to require a REMS when approving a new drug application. FDA also generally considers these factors in determining whether (based on new safety information) a REMS is necessary for a drug that is the subject of an approved application:

Moreover, a REMS with ETASU that would require physician, patient, and pharmacy education for Levaquin could delay access when it is needed urgently to treat patients with serious and potentially life-threatening infections. As Levaquin is indicated for serious infections (e.g., community-acquired pneumonia, pneumonic and septicemic plague, chronic bacterial prostatitis) that may be life-threatening, it is important that certain patients have immediate access to this drug. Therefore, FDA has determined a REMS is not necessary to ensure Levaquin's benefits outweigh its risks at this time.

III. CONCLUSION

For the reasons explained above, your Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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Patrizia Cavazzoni, M.D.
Acting Director
Center for Drug Evaluation and Research

- 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
- The expected benefit of the drug with respect to the disease or condition
- The seriousness of the disease or condition that is to be treated with the drug
- Whether the drug is a new molecular entity
- The expected or actual duration of treatment with the drug
- The estimated size of the population likely to use the drug