CITIZEN PETITION

RE: All Fluoroquinolone antibiotics, including but not limited to:

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

Licensed Name: Cipro, Active Ingredient Ciprofloxacin
NDA 019537
Manufactured by Bayer
License Date: 10/22/1987

Linda Martin, PhD, David Melvin, and Michael Mendoza submit 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.

The submitters of this Citizen Petition respectfully request that the Commissioner of the Food and Drug Administration (FDA) take the following action:

Add language from the Fluoroquinolone Black Box warnings to the top of the drug "MEDICATION GUIDE" for all Fluoroquinolone antibiotics.

A. ACTION REQUESTED

This Citizen Petition requests that the FDA add language from the Fluoroquinolone Black Box warnings to the top of the drug "MEDICATION GUIDE" for all Fluoroquinolone antibiotics, as indicated in the following.

Note: Descriptions of the Black Box warning adverse events (Tendonitis and tendon rupture; Peripheral neuropathy; and Central nervous system effects) in the following language requested by this Citizen Petition are included for additional patient information in order to enhance patient understanding. Adverse event descriptions have been taken directly from the current Fluoroquinolone label "Warnings and Precautions" section.

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS

Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together including:

Tendinitis and tendon rupture

- Tendonitis and tendon rupture in Achilles tendon; rotator cuff (the shoulder); the hand; the biceps; the thumb; and other tendon sites Tendinitis and tendon rupture can occur bilaterally, in both the right and left sides

Peripheral neuropathy

- Peripheral neuropathy: pain; burning; tingling; numbness; weakness; alterations of sensation including light touch, pain, temperature, position sense; vibratory sensation

Central nervous system effects

- Psychiatric: toxic psychoses, hallucinations, paranoia, depression, suicide, suicidal thoughts, anxiety, agitation, restlessness, nervousness, confusion, delirium, disorientation, disturbances in attention, insomnia, nightmares, memory impairment
- Central nervous system: seizures, convulsions, increased intracranial pressure tremors, lightheadedness

Discontinue immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions.

Because fluoroquinolones have been associated with serious adverse reactions, reserve 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

Taking this action to add the above Black Box warnings language to the top of the Fluoroquinolone Medication Guides will:

(1) Improve the quality of Fluoroquinolone safety information provided to patients.

(2) Provide additional drug safety information which will enable patients to make better-informed decisions before consuming the drug.

(3) Improve overall patient safety related to Fluoroquinolones.

B. STATEMENT OF GROUNDS FOR REQUESTED ACTIONS

Grounds for the request to add language from the Fluoroquinolone Black Box warnings to the top of the drug "MEDICATION GUIDE" for all Fluoroquinolones.

Background

The Centers for Disease Control and Prevention (CDC) provides background on Fluoroquinolones:

> "In the United States, nine fluoroquinolones are currently approved for human use. Norfloxacin was the first fluoroquinolone approved for human use (1986), followed by ciprofloxacin (1987), ofloxacin (1990), enoxacin (1991), lomefloxacin (1992), levofloxacin (1996), trovafloxacin (1997), gatifloxacin (1999), and moxifloxacin (1999). Gemifloxacin is currently undergoing clinical investigation in the United States."
> (CDC website, https://www.cdc.gov/hai/settings/lab/quinolones-clinical-laboratory.html)

The FDA FAERS system includes a significant number of Fluoroquinolone adverse event cases, including cases identified as "serious" cases and as "death" cases. FAERS adverse event cases for only two of the nine Fluoroquinolones, Levaquin/levofloxacin and Cipro/ciprofloxacin, are indicated in the following chart.

	Total FAERS Adverse Event Cases As of June 30, 2023	**FAERS "Serious" Adverse Event Cases As of June 30, 2023**	**FAERS "Death" Adverse Event Cases As of June 30, 2023**
Levaquin/ levofloxacin	54,454	46,455	3,612
Cipro/ ciprofloxacin	51,662	42,562	3,604
Total	**106,116**	**89,017**	**7,216**

As noted, the above chart only highlights adverse events FAERS data for only two Fluoroquinolones: Levaquin/levofloxacin and Cipro/ciprofloxacin. The above data would be significantly higher when considering adverse events for all nine Fluoroquinolones.

Additionally, given that the FDA acknowledges that only approximately 10% of adverse events are reported to FAERS, the actual number of Fluoroquinolone adverse events is likely closer to 10 times higher.

Assuming only 10% of adverse events are reported to FAERS, the actual number of adverse event cases for just these two Fluoroquinolones (Levaquin/levofloxacin and Cipro/ciprofloxacin) likely exceed one million. Likewise, the actual number of "serious" cases is likely closer to 900,000 and the actual number of "death" cases is likely closer to 70,000.

November 5, 2015 FDA Advisory Committee Meeting Regarding Fluoroquinolones

On November 5, 2015, the FDA held a Joint Meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.
(FDA website. https://www.fda.gov/media/104060/download)

After presentations by consumers; representatives from Johnson & Johnson/Janssen and Bayer; and the FDA, the FDA Advisory Committee voted overwhelmingly that the existing Fluoroquinolones drug labels were not adequate.

1. Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial sinusitis (ABS)?	NO: 21 YES: 0 ABSTAIN: 0
2. Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease (ABECB-COPD)?	NO: 18 YES: 2 ABSTAIN: 1
3. VOTE: Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of uncomplicated urinary tract infection (uUTI)?	NO: 20 YES: 1 ABSTAIN: 0

On July 26, 2016, the Fluoroquinolone drug manufacturers, Johnson & Johnson/Janssen and Bayer, updated the Black Box warnings for Levaquin and Cipro as follows, using Levaquin as an example.

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS See full prescribing information for complete boxed warning.

Fluoroquinolones, including LEVAQUIN®, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:
o Tendinitis and tendon rupture (5.2)
o Peripheral neuropathy (5.3)
o Central nervous system effects (5.4)

Discontinue LEVAQUIN® immediately and avoid the use of fluoroquinolones, including LEVAQUIN®, in patients who experience any of these serious adverse reactions (5.1)

Fluoroquinolones, including LEVAQUIN®, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis [see Warnings and Precautions (5.5)].

Because fluoroquinolones, including LEVAQUIN®, have been associated with serious adverse reactions (5.1-5.15), reserve LEVAQUIN® for use in patients who have no alternative treatment options for the following indications:
o Uncomplicated urinary tract infection (1.12)
o Acute bacterial exacerbation of chronic bronchitis (1.13)
o Acute bacterial sinusitis (1.14)

(drugs@FDA, Levaquin label, July 26, 2016, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020634s073lbl.pdf

In a July 26, 2016 FDA News Release, "The FDA updates warnings for fluoroquinolone antibiotics," referencing the above label change, Edward Cox, M.D., Director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research, stated that "Fluoroquinolones have risks and benefits that should be considered very carefully." He added that "It's important that both health care providers and patients are aware of both the risks and benefits of fluoroquinolones and make an informed decision about their use." (FDA website, 7/26/2016, https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics)

The FDA News Release further explained:

> The [Fluoroquinolone] labeling changes include an updated Boxed Warning and revisions to the Warnings and Precautions section of the label about the risk of disabling and potentially irreversible adverse reactions that can occur together. The label also contains new limitation-of-use statements to reserve fluoroquinolones for patients who do not have other available treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections. The patient Medication

> Guide that is required to be given to the patient with each fluoroquinolone prescription describes the safety issues associated with these medicines.
>
> (FDA website, 7/26/2016, https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics)

Although the FDA News Release stated that "the patient Medication Guide that is required to be given to the patient with each fluoroquinolone prescription describes the safety issues associated with these medicines," the drug manufacturers Johnson & Johnson/Janssen and Bayer failed to add the Black Box warning language to the Medication Guide.

Thus, the "the patient Medication Guide that is required to be given to the patient with each fluoroquinolone prescription" actually does not describe "the safety issues associated with these medicines" because the Fluoroquinolone Medication Guides lack the Black Box warning language.

FDA Guidance on "Medication Guides"

As defined by the FDA, "a Medication Guide is patient labeling that is part of the FDA-approved prescription drug labeling for certain prescription drugs when the FDA determines that:

- Patient labeling could help prevent serious adverse reactions
- The drug 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, or
- Patient adherence to directions for use is crucial to the drug's effectiveness.

> (FDA website, https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/patient-labeling-resources#:~:text=A%20Medication%20Guide%20is%20patient%20labeling%20that%20is,for%20use%20is%20crucial%20to%20the%20drug's%20effectiveness.)

As described November 2011 by the FDA in "Guidance Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)," under the heading, "Medication Guide Regulations:"

> In 1998, FDA issued final regulations establishing requirements for the distribution of patient labeling for certain prescription drugs and biological products used primarily on an outpatient basis without direct supervision by a healthcare professional (63 FR 66378, December 1, 1998). These regulations, codified in 21 CFR part 208, apply to certain drug and biological products that FDA determines pose a serious and significant public health concern requiring the distribution of FDA-approved patient medication information that is necessary to patients' safe and effective use of the drug products (a Medication Guide).
>
> (FDA website, https://www.fda.gov/media/79776/download)

Fluoroquinolones contain a Medication Guide. Thus, by definition, Fluoroquinolones are "products that FDA determines pose a serious and significant public health concern requiring the distribution of FDA-approved patient medication information that is necessary to patients' safe and effective use of the drug products (a Medication Guide)."

As further described in the FDA's November 2011 document:

> "Section 208.1(c) authorizes FDA to require a Medication Guide if FDA determines one or more of the following circumstances exist:
>
> (1) The drug product is one for which patient labeling could help prevent serious adverse effects.
>
> (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 risks could affect patients' decision to use, or continue to use, the product.
>
> (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Thus, by definition, Fluoroquinolones:

> (1) Are drugs for which patient labeling could help prevent serious adverse effects.
>
> (2) Are drugs that have serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, the product.
>
> (3) Have Medication Guides which are important to health and patient adherence to directions for use and is crucial to the drugs' effectiveness.

Therefore, it is critically important for the Fluoroquinolone "Medication Guides" to be robust and accurate.

<u>Current Fluoroquinolone "Medication Guides" are Inadequate and Misleading</u>

The current Fluoroquinolone "Medication Guides" do not provide adequate information for patients about potential adverse events. In fact, the current Fluoroquinolone "Medication Guides" are misleading.

Of particular importance is that the Fluoroquinolone "Medication Guides," developed by the drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, failed to include the information found in the Fluoroquinolone Black Box warnings.

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

> "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)

By definition, the current Fluoroquinolone Black Box Warnings indicate adverse reactions "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."

However, Fluoroquinolone drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, have failed to include the Black Box warning language with describes adverse reactions "so serious in proportion to the potential benefit from the drug" in the "Medication Guides."

Given that the FDA describes the seriousness of Black Box warnings, it is abundantly clear that language from the current Fluoroquinolone Black Box warnings should also be included in the Medication Guides" for all Fluoroquinolones.

Failure to Warn of Potentially Serious, Disabling, Irreversible Adverse Events

Drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, developed and are currently using "Medication Guides" which fail to inform patients that:

> Fluoroquinolones 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 immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions.

Current Fluoroquinolone "Medication Guides" fail to warn patients that consuming Fluoroquinolones may result in disabling, permanent side effects.

Drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, should immediately add language from the Black Box warnings, as requested by this Citizen Petition, to the "Medication Guides."

Failure to Warn That Fluoroquinolones are Last Resort for Routine Infections

Drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, developed and are currently using "Medication Guides" which fail to inform patients that: Fluoroquinolones should be reserved 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

Current Fluoroquinolone "Medication Guides" fail to warn patients that Fluoroquinolones should not be prescribed for uncomplicated urinary tract infection, acute bacterial exacerbation of chronic bronchitis, or acute bacterial sinusitis unless no other alternative antibiotic is appropriate.

Drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, should immediately add language from the Black Box warnings, as requested by this Citizen Petition, to the "Medication Guides."

Failure to Allow Patients to Have Informed Consent

A foundation of the American healthcare system is informed consent. Patients should be provided a full description of potential Fluoroquinolone adverse events prior to consuming a Fluoroquinolone.

Although the FDA wrote, "Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors" related to informed consent for research, the following are the general concepts put forth by the FDA about informed consent. The following language has been modified to be appropriate for the scenario of patients prescribed a medication, such as a Fluoroquinolone.

> Informed consent involves providing a patient with adequate information to allow for an informed decision about consuming a drug. Informed consent also involves facilitating the patient's understanding of information about the drug's potential adverse events, providing adequate opportunity for the patient to consider whether to consume the drug.
> (FDA website, https://www.fda.gov/media/88915/download)

Drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, should immediately add language from the Black Box warnings, as requested by this Citizen Petition, to the "Medication Guides" in order to allow patients to essentially give a greater level of informed consent when consuming Fluoroquinolones.

FDA Adverse Event Reporting System (FAERS) Data Related to Citizen Petition Request

The FDA FAERS system includes significant Levaquin/levofloxacin adverse event cases, including cases identified as "serious" cases and as "death" cases, as indicated in the following chart. The following chart includes adverse event cases related to categories included in the Black Box warning: Tendonitis/Tendon Rupture, Peripheral Neuropathy, and Central Nervous System.

Black Box Warning Adverse Event Categories	**Levaquin/levofloxacin FAERS Cases As of June 30, 2023**	**Levaquin/levofloxacin "Serious" Cases As of June 30, 2023**
Tendonitis/Tendon Rupture	6,246	5,856
Peripheral Neuropathy	2,784	2,600
Central Nervous System	14,044	12,548
Total	**23,074**	**21,004**

Given that the FDA acknowledges that only approximately 10% of adverse events are reported to FAERS, the actual number of Levaquin/levofloxacin adverse events for Black Box warning categories is likely closer to 10 times higher.

Assuming only 10% of adverse events are reported to FAERS, the actual number of Levaquin/levofloxacin adverse events for Black Box warning categories is likely closer to 200,000. Likewise, the actual number of "serious" cases is likely closer to 200,000.

Similarly, the FDA FAERS system includes significant Cipro/ciprofloxacin adverse event cases, including cases identified as "serious" cases and as "death" cases, as indicated in the following chart.

Black Box Warning Adverse Event Categories	**Cipro/ciprofloxacin FAERS Cases As of June 30, 2023**	**Cipro/ciprofloxacin FAERS "Serious" Cases As of June 30, 2023**
Tendonitis/Tendon Rupture	3,799	2,992
Peripheral Neuropathy	2,453	2,354
Central Nervous System	14,157	12,940
Total	**20,409**	**18,286**

Given that the FDA acknowledges that only approximately 10% of adverse events are reported to FAERS, the actual number of Cipro/ciprofloxacin adverse events for Black Box warning categories is likely closer to 10 times higher.

Assuming only 10% of adverse events are reported to FAERS, the actual number of Cipro/ciprofloxacin adverse events for Black Box warning categories is likely closer to 200,000. Likewise, the actual number of "serious" cases is likely closer to 180,000.

Based, in part, on the thousands of adverse events reported in FAERS related to the categories included in the Black Box warnings, drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, should immediately add language from the Black Box warnings, as requested by this Citizen Petition, to the "Medication Guides."

Urgency for This Citizen Petition Request to be Approved

As noted, on July 26, 2016, the Fluoroquinolone drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, updated the Black Box warnings to include the language highlighted in this Citizen Petition.

On July 26, 2016, this Black Box warning language was also added to the Fluoroquinolone "Warnings and Precautions" label sections.

But this Black Box warning language was not added to the Fluoroquinolone "Medication Guides."

Thus, for the past seven years, patients have not received the critically important information about potentially serious, disabling, irreversible adverse events contained in the Black Box warnings.

Dawn Mendoza, wife of Michael Mendoza who is a submitter of this Citizen Petition, ended her life by suicide just four days after consuming Cipro in 2019. When Dawn Mendoza was prescribed Cipro in 2019, the Cipro Black Box warning information was not at the top of the Medication Guide. This is true today, as it has been true every day since the Black Box warnings were added to the labels of Cipro and the other Fluoroquinolones in 2008.

And, for the past seven years, patients have not received the critically important information that Fluoroquinolones are not recommended for urinary tract infection, bronchitis, or sinusitis unless there is no other appropriate alternative, as indicated in the Black Box warnings.

For seven years, patients who consumed Fluoroquinolones had no idea that these drugs can result in serious, disabling, irreversible adverse events or that these drugs are not recommended for urinary tract infection, bronchitis, or sinusitis unless there is no other appropriate alternative.

As documented herein, there is clearly an urgency to approve this Citizen Petition request so that patients can read this critically important Black Box warning information at the top of the "Medication Guide" when they receive a Fluoroquinolone prescription.

Some may argue that providing this information—already found in the Black Box warning and "Warnings and Precautions" sections of the Fluoroquinolone labels—may discourage patients from consuming a prescribed Fluoroquinolone. But this argument is not a valid excuse for failing to tell patients that Fluoroquinolones are associated with "disabling and potentially irreversible serious adverse reactions."

Patients expect and deserve to receive accurate, robust, comprehensive information about the Fluoroquinolone prescribed, including about "disabling and potentially irreversible serious adverse reactions."

As described previously by Dr. Cox, Director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research, "Fluoroquinolones have risks and benefits that should be considered very carefully." Currently, it is impossible for patients to carefully consider the

risks and benefits of taking a Fluoroquinolone because the "Medication Guides" lack the Black Box warnings language.

As Dr. Cox additionally stated, "It's important that both health care providers and patients are aware of both the risks and benefits of fluoroquinolones and make an informed decision about their use." Currently it is impossible for patients to be aware of the risks and benefits of Fluoroquinolones in order to make an informed decision about of taking one of these drugs because the "Medication Guides" lack the Black Box warnings language.

The Fluoroquinolone drug manufacturers, including Johnson & Johnson/Janssen for Levaquin and Bayer for Cipro, should immediately be required to add the Black Box warning language to the Fluoroquinolone "Medication Guides," as requested by this Citizen Petition.

D. ENVIRONMENTAL IMPACT

This Citizen Petition's request will not have an impact on the environment.

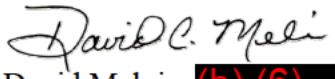
E. ECONOMIC IMPACT

This Citizen Petition's request will not have an economic impact.

F. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information 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,



David Melvin: (b) (6)

Linda Martin, PhD
Michael Mendoza