DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078712

LABELING ORDER

Sandoz, Inc.
Attention: Alison Sherwood
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA or Act) for Ciprofloxacin Extended-release Tablets, 500 mg.

On June 27, 2013, we sent you a letter pursuant to section 505(o)(4) of the FDCA that required safety related changes to the labeling of Ciprofloxacin Extended-release Tablets to address the risk of irreversible peripheral neuropathy. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or to notify FDA that you do not believe a labeling change is warranted, and to submit a statement detailing the reasons why such a change is not warranted.

In your July 3, 2013 letter, you explained the reasons why you believe a labeling change to address the risk of irreversible peripheral neuropathy is not warranted for your Ciprofloxacin Extended-release Tablets; specifically that you are not currently marketing your product under your approved ANDA application. However, as explained in the June 27, 2013, safety labeling change notification letter, requirements under section 505(o)(4) of the Act apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug under an NDA, unless approval of your application has been withdrawn in the Federal Register. Therefore, even if you are not currently marketing your product, because your application has not been withdrawn, you are required to comply with the safety labeling change requirements in section 505(o)(4) of the Act.

Pursuant to the authority in section 505(o)(4)(E) of the Act, we are ordering you to make all of the changes in the labeling listed in the June 27, 2013 letter (attached). Thus, a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the June 27, 2013, letter must be received by FDA by August 29, 2013, for your Ciprofloxacin Extended-release Tablets.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, as outlined in section 505(o)(4)(F) of the Act, by August 19, 2013, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level." The appeal should be submitted as correspondence to your ANDA referenced above. Identify the submission as
"**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submissions should be sent to:

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Building 22, Room 6465
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Carrie Lemley
Labeling Project Manager
Office of Generic Drugs
Food and Drug Administration
7520 Standish Place
Rockville, MD 20855

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Amy Bertha, CDER Formal Dispute Resolution Project Manager, at (301) 796-1647. An appeal received by the Agency later than August 19, 2013, will not be entertained.

As explained in section 505(o)(4)(G) of the Act, failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, included but not limited to seizure of your product and injunction.

If you have any questions, call Carrie Lemley, Labeling Project Manager, at (240) 276-8986.

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Acting Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE: Safety Labeling Change Notification Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078712

SAFETY LABELING CHANGE NOTIFICATION

Sandoz Inc.
Attention: Alison Sherwood
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ciprofloxacin Extended-release Tablets, 500 mg.

Section 505(o)(4) also authorizes FDA to require the holder of an approved application under section 505(j) (an abbreviated new drug application or ANDA) to make safety related label changes based upon new safety information if the same drug approved under section 505(b) is not currently marketed. You are the holder of an application which references a drug approved under section 505(b) that is not withdrawn and not currently marketed.

Since Ciprofloxacin Extended-release Tablets was approved on December 11, 2007 we have become aware of the serious safety risk of irreversible peripheral neuropathy. This is based on our review of post-marketing adverse event reports from the Adverse Event Reporting System (AERS) and published case reports in the scientific literature. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for the systemic fluoroquinolone antibacterial class as follows: (underlined text=addition, ~~strikethrough text~~=deletion)

WARNINGS
Peripheral Neuropathy
(b) (4) Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including ciprofloxacin. Symptoms may occur soon after initiation of ciprofloxacin and may be irreversible. Ciprofloxacin should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness (b) (4) or other alterations

in sensations including light touch, pain, temperature, position sense, or vibratory sensation [redacted (b) (4)]

PRECAUTIONS
Information for Patients
That peripheral neuropathies have been associated with ciprofloxacin use, that symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should immediately discontinue ciprofloxacin [redacted (b) (4)] and contact their physician.

ADVERSE REACTIONS
Postmarketing Adverse Event Reports
Peripheral neuropathy that may be irreversible

MEDICATION GUIDE
(Under "**What are the possible side effects of Ciprofloxacin**?")
Changes in sensation and [redacted (b) (4)]-nerve damage (peripheral neuropathy). Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including ciprofloxacin. Stop ciprofloxacin and talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs or feet: pain, burning, tingling, numbness, weakness. The nerve damage may be permanent. [redacted (b) (4)]

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement (PAS) proposing changes to the approved labeling in accordance with the above direction and pay the required PAS fee as required by the Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

Also, we have recently reviewed a literature report (Hinkle et al. Bilateral uveitis associated with fluoroquinolone therapy. Cutan Ocul Toxicol. 2012 Jun;31(2):111-6) and post-marketing adverse event reports from the Adverse Event Reporting System regarding uveitis associated with fluoroquinolone use . Based on our review, we request the addition of uveitis to the **ADVERSE REACTIONS Section, Postmarketing Adverse Event Reports subsection.**

If you have any questions, call Carrie Lemley, Labeling Project Manager, at (240) 276-8986.

Sincerely,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

06/27/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEITH O WEBBER
08/19/2013