DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21744/S-016

SUPPLEMENT APPROVAL

Depomed, Inc.
Attention: Ms. Hayley Welton, RAC
Associate Director, Regulatory Affairs
1360 O’Brien Drive
Menlo Park, CA 94025

Dear Ms. Welton:

Please refer to your Supplemental New Drug Application (sNDA) dated December 21, 2010, and received December 22, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Proquin® XR (ciprofloxacin) Extended-Release Tablets, 500 mg.

We acknowledge receipt of your amendments dated February 8, 2011 and February 11, 2011.

(b) (4) [redacted]

We also refer to our letter dated November 15, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for all fluoroquinolone products. This information pertains to the risk of fluoroquinolone-associated myasthenia gravis exacerbation, which is a potentially life-threatening event and may require ventilatory support.

This supplemental new drug application provides for revisions to the labeling for Proquin® XR (ciprofloxacin) Extended-Release. The agreed upon changes to the language included in our November 15, 2010, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough)~~.

I. HIGHLIGHTS

Proquin® XR (ciprofloxacin) Extended-Release Tablets, 500 mg*
***present as 582 mg of ciprofloxacin hydrochloride monohydrate**
~~**Proquin® XR (ciprofloxacin hydrochloride) Tablets, 500 mg**~~
Initial U.S. Approval: 1987

WARNING: TENDINITIS/TENDON RUPTURE
See full prescribing information for complete boxed warning. Fluoroquinolones, including Proquin XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. The risk further increased in patients over 60 years of age, taking corticosteroid drugs, and in patients

with kidney, heart and lung transplant recipients (5.1).
Fluroquinolones, including Proquin XR, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Proquin XR in patients with known history of myasthenia gravis (See Warnings).

_______________ DOSAGE FORMS AND STRENGTHS ______________

Extended release tablets: 500 mg* of ciprofloxacin ~~hydrochloride~~ (3)
*present as 582 mg of ciprofloxacin hydrochloride monohydrate

II. Full Prescribing: Content: Numbers have been revised accordingly.

III. BOXED WARNING

WARNING:
Fluoroquinolones, including Proquin®XR, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).
Fluoroquinolones, including Proquin®XR, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Proquin®XR in patients with known history of myasthenia gravis (See Warnings).

IV. 3 DOSAGE FORMS AND STRENGTHS

Extended release tablets: 500 mg* of ciprofloxacin ~~hydrochloride~~
*present as 582 mg of ciprofloxacin hydrochloride monohydrate

V. 5 WARNINGS AND PRECAUTIONS

5.2 Exacerbation of myasthenia gravis

Fluoroquinolones, including Proquin XR, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid **Proquin XR** in patients with known history of myasthenia gravis. [See **PRECAUTIONS/Information for Patients and ADVERSE REACTIONS/Reported Post-Marketing Adverse Events with Other Formulations of Ciprofloxacin**).

VI. 11 DESCRIPTION

Proquin XR (ciprofloxacin hydrochloride monohydrate) extended-release tablets contain 582 mg of ciprofloxacin hydrochloride monohydrate, a synthetic broad-spectrum fluoroquinolone antimicrobial agent for oral administration, which is equivalent to 500 mg of ciprofloxacin.
Ciprofloxacin hydrochloride monohydrate is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride monohydrate. The molecular

weight the ciprofloxacin hydrochloride monohydrate is 385.82. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:

Proquin XR is available as 500 mg (ciprofloxacin hydrochloride monohydrate equivalent) tablets, utilizing AcuForm®™ delivery technology. Proquin XR tablets are blue film-coated and oval-shaped. The inactive ingredients are povidone, magnesium stearate, polyethylene oxide, and film coating (Opadry® Blue).

VII. 17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Medication Guide* ~~(17.14)~~

17.3 Myasthenia Gravis Syndrome

Fluoroquinolones like Proquin XR may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if you have any worsening muscle weakness or breathing problems.

17.12 Use of Proquin XR Sample Pack

Advise the patient that the sample pack contains only one dose for the first day of treatment with Proquin® XR. Complete treatment requires 3 doses. The patient must fill a prescription for the remaining two doses.

VIII. Medication guide:

a. In the section "**What is the most important information I should know about Proquin®XR?**" The following has been added as the last bulleted paragraph:

- **Worsening of myasthenia gravis (a disease which causes muscle weakness).** Fluoroquinolones like **Proquin®XR** may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

See the section **"What are the possible side effects of Proquin®XR?"** for more information about side effects.

b. In the section **"What should I tell my healthcare provider before taking Proquin®XR?"** The following has been revised:

What should I tell my healthcare provider before taking Proquin®XR?

See **"What is the most important information I should know about Proquin®XR?"**

Before taking Proquin® XR, tell your healthcare provider if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)
- have nerve problems

- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have a history of seizures
- have kidney problems
- have low blood potassium (hypokalemia)
- have rheumatoid arthritis (RA) or other history of joint problems
- have trouble swallowing pills
- are pregnant or planning to become pregnant. It is not known if Proquin® XR will harm your unborn child.
- are breastfeeding or planning to breastfeed. Proquin® XR can pass into your breast milk and may harm your baby. You and your healthcare provider should decide whether you will take Proquin® XR or breastfeed. You should not do both. See "What should I avoid while taking Proquin XR?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal and dietary supplements. Proquin® XR and certain other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®). Serious reactions, including death can happen in people who take Proquin XR and theophylline. Your healthcare provider may change your dose of theophylline and perform blood test to check your theophylline level if you take Proquin XR and theophylline.

c. In the section **"What should I avoid while taking Proquin® XR?"** The following has been revised:

What should I avoid while taking Proquin® XR?

- Proquin® XR can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how Proquin® XR affects you.

- Avoid sunlamps, tanning beds, and try to limit your time in the sun. Proquin® XR can make your skin sensitive to the sun (photosensitivity) and the light from the sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking Proquin® XR, call your healthcare provider right away. You should use a sunscreen, and wear a hat and clothes that cover your skin if you have to be in sunlight.

- Avoid breastfeeding during treatment with Proquin XR. If you are breastfeeding, you should either stop breastfeeding, or pump and throw away the milk **during treatment and for 24 hours after your last dose** of Proquin XR. See "What should I tell my doctor before taking Proquin XR?"

d. Additional editorial revisions to the medication guide

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

OZLEM A BELEN
02/25/2011