CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-537/S-070

Trade Name: Cipro

Generic Name: ciprofloxacin hydrochloride

Sponsor: Bayer Healthcare

Approval Date: 4/27/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

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Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-070
NDA 19-847/S-044
NDA 19-857/S-051
NDA 20-780/S-028
NDA 21-473/S-025

Bayer Pharmaceuticals Corporation
Attention: Janet Herrington, Ph.D.
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, New Jersey 07045-1000

Dear Dr. Herrington:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Drug Product Name	**NDA Number**	**Supplement number**	**Date of supplement**	**Date of receipt**
CIPRO® (ciprofloxacin hydrochloride) Tablets	19-537	S-070	November 3, 2008	November 3, 2008
CIPRO® IV (ciprofloxacin) 1% Solution in Vials	19-847	S-044	November 3, 2008	November 14, 2008
CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose	19-857	S-051	November 3, 2008	November 14, 2008
CIPRO® (ciprofloxacin) Oral Suspension	20-780	S-028	November 3, 2008	November 14, 2008
CIPRO® XR (ciprofloxacin extended-release tablets)	21-473	S-025	November 3, 2008	November 14, 2008

We acknowledge receipt of your submissions dated February 19, 2009 and March 27, 2009.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

Since Cipro® was approved on October 22, 1987, we have become aware of additional information about the risk of tendon-related adverse events as described in our July 7, 2008 letter. This

information was not available when Cipro® was granted marketing authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA notified you in our July 7, 2008, letter that the development of a Medication Guide was required as provided for under 21 CFR Part 208. In response, you converted your previously approved patient package insert to a Medication Guide and revised it to include the new safety information. Pursuant to 21 CFR Part 208, FDA has determined that Cipro® poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Cipro®. FDA has determined that Cipro® is a product that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use Cipro®. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Cipro®.

Your proposed REMS, submitted on November 3, 2008 and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your February 19, 2009 and March 27, 2009 submissions.

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of Cipro®
b. A report on periodic assessments of the distribution and dispending of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 19-537, NDA 19-847, NDA 19-857, NDA 20-780, and
NDA 21-473 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 19-537, NDA 19-847, NDA 19-857,
NDA 20-780, and NDA 21-473
PROPOSED REMS MODIFICATION
< other supplement identification > [if included]
<REMS ASSESSMENT> [if included]

If you do not submit electronically, please send 5 copies of submissions containing REMS assessments or proposed modifications of the REMS.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 19-537/S-070, NDA 19-847/S-044, NDA 19-857/S-051, NDA 20-780/S-028, and NDA 21-473/S-025."**

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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., Acting Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure: REMS
Medication Guide

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

/s/

Ozlem Belen

4/27/2009 02:59:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

LABELING

MEDICATION GUIDE
CIPRO® (Sip-row)
(ciprofloxacin hydrochloride)
TABLETS
CIPRO® (Sip-row)
(ciprofloxacin)
ORAL SUSPENSION
CIPRO® XR (Sip-row)
(ciprofloxacin extended-release tablets)
CIPRO® I.V. (Sip-row)
(ciprofloxacin)
For Intravenous Infusion

Read the Medication Guide that comes with CIPRO® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about CIPRO?

CIPRO belongs to a class of antibiotics called fluoroquinolones. CIPRO can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take CIPRO.

Tendon rupture or swelling of the tendon (tendinitis)

- Tendons are tough cords of tissue that connect muscles to bones.
- Pain, swelling, tears and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites can happen in people of all ages who take fluoroquinolone antibiotics, including CIPRO. The risk of getting tendon problems is higher if you:
  - are over 60 years of age
  - are taking steroids (corticosteroids)
  - have had a kidney, heart or lung transplant
- Swelling of the tendon (tendinitis) and tendon rupture (breakage) have also happened in patients who take fluoroquinolones who do not have the above risk factors.
- Other reasons for tendon ruptures can include:
  - physical activity or exercise
  - kidney failure
  - tendon problems in the past, such as in people with rheumatoid arthritis (RA)

- Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking CIPRO until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the risk of tendon rupture with continued use of CIPRO. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
- Tendon rupture can happen while you are taking or after you have finished taking CIPRO. Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
- Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:
  - hear or feel a snap or pop in a tendon area
  - bruising right after an injury in a tendon area

    - unable to move the affected area or bear weight
- See the section **"What are the possible side effects of CIPRO?"** for more information about side effects.

What is CIPRO?

CIPRO is a fluoroquinolone antibiotic medicine used to treat certain infections caused by certain germs called bacteria.

Children less than 18 years of age have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking CIPRO. CIPRO should not be used as the first choice of antibiotic medicine in children under 18 years of age.
CIPRO Tablets, CIPRO Oral Suspension and CIPRO I.V. should not be used in children under 18 years old, except to treat specific serious infections, such as complicated urinary tract infections and to prevent anthrax disease after breathing the anthrax bacteria germ (inhalational exposure). It is not known if CIPRO XR is safe and works in children under 18 years of age.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including CIPRO, do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking CIPRO.

Who should not take CIPRO?

Do not take CIPRO if you:

- have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in CIPRO. Ask your healthcare provider if you are not sure. See the list of ingredients in CIPRO at the end of this Medication Guide.
- also take a medicine called tizanidine (Zanaflex®). Serious side effects from tizanidine are likely to happen.

What should I tell my healthcare provider before taking CIPRO?

See **"What is the most important information I should know about CIPRO?"**

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- 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. You may need a lower dose of CIPRO if your kidneys do not work well.
- 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 CIPRO will harm your unborn child.

- are breast-feeding or planning to breast-feed. CIPRO passes into breast milk. You and your healthcare provider should decide whether you will take CIPRO or breast-feed.

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

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take CIPRO or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See **"What are the possible side effects of CIPRO?"**
- a blood thinner (warfarin, Coumadin®, Jantoven®)
- tizanidine (Zanaflex®). You should not take CIPRO if you are already taking tizanidine. See **"Who should not take CIPRO?"**
- theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®)
- glyburide (Micronase®, Glynase®, Diabeta®, Glucovance®). See **"What are the possible side effects of CIPRO?"**
- phenytoin (Fosphenytoin Sodium®, Cerebyx®, Dilantin-125®, Dilantin®, Extended Phenytoin Sodium®, Prompt Penytoin Sodium®, Phenytek®)
- products that contain caffeine
- a medicine to control your heart rate or rhythm (antiarrhythmics) See **"What are the possible side effects of CIPRO?"**
- an anti-psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See **"What is the most important information I should know about CIPRO?"**
- methotrexate (Trexall®)
- Probenecid (Probalan®, Col-probenecid®)
- Metoclopromide (Reglan®, Reglan ODT®)
- Certain medicines may keep CIPRO Tablets, CIPRO Oral Suspension from working correctly. Take CIPRO Tablets and Oral Suspension either 2 hours before or 6 hours after taking these products:
    - an antacid, multivitamin, or other product that has magnesium, calcium, aluminum, iron, or zinc
    - sucralfate (Carafate®)
    - didanosine (Videx®, Videx EC®)

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take CIPRO?

- Take CIPRO exactly as prescribed by your healthcare provider.
- Take CIPRO Tablets in the morning and evening at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you can not swallow the tablet whole.

- Take CIPRO Oral Suspension in the morning and evening at about the same time each day. Shake the CIPRO Oral Suspension bottle well each time before use for about 15 seconds to make sure the suspension is mixed well. Close the bottle completely after use.
- Take CIPRO XR one time each day at about the same time each day. Swallow the tablet whole. Do not split, crush or chew the tablet. Tell your healthcare provider if you can not swallow the tablet whole.
- CIPRO I.V. is given to you by intravenous (I.V.) infusion into your vein, slowly, over 60 minutes, as prescribed by your healthcare provider.
- CIPRO can be taken with or without food.
- CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone, but may be taken with a meal that contains these products.
- Drink plenty of fluids while taking CIPRO.
- Do not skip any doses, or stop taking CIPRO even if you begin to feel better, until you finish your prescribed treatment, unless:
    - you have tendon effects (see **"What is the most important information I should know about CIPRO?"**),
    - you have a serious allergic reaction (see **"What are the possible side effects of CIPRO?"**), or
    - your healthcare provider tells you to stop.
- This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to CIPRO. If this happens, CIPRO and other antibiotic medicines may not work in the future.
- If you miss a dose of CIPRO Tablets or Oral Suspension, take it as soon as you remember. Do not take two doses at the same time, and do not take more than two doses in one day.
- If you miss a dose of CIPRO XR, take it as soon as you remember. Do not take more than one dose in one day.
- If you take too much, call your healthcare provider or get medical help immediately.

If you have been prescribed CIPRO Tablets, CIPRO Oral Suspension or CIPRO I.V. after being exposed to anthrax:

- CIPRO Tablets, Oral Suspension and I.V. has been approved to lessen the chance of getting anthrax disease or worsening of the disease after you are exposed to the anthrax bacteria germ.
- Take CIPRO exactly as prescribed by your healthcare provider. Do not stop taking CIPRO without talking with your healthcare provider. If you stop taking CIPRO too soon, it may not keep you from getting the anthrax disease.
- Side effects may happen while you are taking CIPRO Tablets, Oral Suspension or I.V. When taking your CIPRO to prevent anthrax infection, you and your healthcare provider should talk about whether the risks of stopping CIPRO too soon are more important than the risks of side effects with CIPRO.
- If you are pregnant, or plan to become pregnant while taking CIPRO, you and your healthcare provider should decide whether the benefits of taking CIPRO Tablets, Oral Suspension or I.V. for anthrax are more important than the risks.

What should I avoid while taking CIPRO?

- CIPRO 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 CIPRO affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. CIPRO can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could

get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking CIPRO, 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.

What are the possible side effects of CIPRO?

CIPRO can cause side effects that may be serious or even cause death. See **"What is the most important information I should know about CIPRO?"**

Other serious side effects of CIPRO include:

- **Central Nervous System effects:** Seizures have been reported in people who take fluoroquinolone antibiotics including CIPRO. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking CIPRO will change your risk of having a seizure.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of CIPRO. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:
  - feel dizzy
  - seizures
  - hear voices, see things, or sense things that are not there (hallucinations)
  - feel restless
  - tremors
  - feel anxious or nervous
  - confusion
  - depression
  - trouble sleeping
  - nightmares
  - feel more suspicious (paranoia)
  - suicidal thoughts or acts

- **Serious allergic reactions:** Allergic reactions can happen in people taking fluoroquinolones, including CIPRO, even after only one dose. Stop taking CIPRO and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
  - hives
  - trouble breathing or swallowing
  - swelling of the lips, tongue, face
  - throat tightness, hoarseness
  - rapid heartbeat
  - faint
  - yellowing of the skin or eyes. Stop taking CIPRO and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to CIPRO (a liver problem).
- **Skin rash:** Skin rash may happen in people taking CIPRO even after only one dose. Stop taking CIPRO at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to CIPRO.
- **Serious heart rhythm changes** (QT prolongation and torsade de pointes): Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. CIPRO may cause a rare heart problem known as prolongation of the

QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:
  - who are elderly
  - with a family history of prolonged QT interval
  - with low blood potassium (hypokalemia)
  - who take certain medicines to control heart rhythm (antiarrhythmics)
- **Intestine infection** (Pseudomembranous colitis): Pseudomembranous colitis can happen with most antibiotics, including CIPRO. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.
- **Changes in sensation and possible nerve damage** (Peripheral Neuropathy): Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including CIPRO. 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

  CIPRO may need to be stopped to prevent permanent nerve damage.
- **Low blood sugar** (hypoglycemia): People who take CIPRO and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar (hypoglycemia) which can sometimes be severe. Tell your healthcare provider if you get low blood sugar with CIPRO. Your antibiotic medicine may need to be changed.
- **Sensitivity to sunlight** (photosensitivity): See **"What should I avoid while taking CIPRO?"**
- **Joint Problems:** Increased chance of problems with joints and tissues around joints in children under 18 years old. Tell your child's healthcare provider if your child has any joint problems during or after treatment with CIPRO.

The most common side effects of CIPRO include:
- nausea
- headache
- diarrhea
- vomiting
- vaginal yeast infection
- changes in liver function tests
- pain or discomfort in the abdomen

These are not all the possible side effects of CIPRO. Tell your healthcare provider about any side effect that bothers you, or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CIPRO?
- CIPRO Tablets

  - Store CIPRO below 86°F (30°C)
- CIPRO Oral Suspension
  - Store CIPRO Oral Suspension below 86°F (30°C) for up to 14 days
  - Do not freeze
  - After treatment has been completed, any unused oral suspension should be safely thrown away
- CIPRO XR
  - Store CIPRO XR at 59°F to 86°F (15°C to 30°C)

Keep CIPRO and all medicines out of the reach of children.

General Information about CIPRO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CIPRO for a condition for which it is not prescribed. Do not give CIPRO to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about CIPRO. If you would like more information about CIPRO, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CIPRO that is written for healthcare professionals. For more information go to www.CIPRO.com or call 1-800-526-4099.

What are the ingredients in CIPRO?

- CIPRO Tablets
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, and polyethylene glycol
- CIPRO Oral Suspension:
  - Active ingredient: ciproflxacin
  - Inactive ingredients: The components of the suspension have the following compositions: Microcapsules—ciprofloxacin, povidone, methacrylic acid copolymer, hypromellose, magnesium stearate, and Polysorbate 20. Diluent—medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.
- CIPRO XR:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.
- CIPRO I.V.:
  - Active ingredient: ciprofloxacin
  - Inactive ingredients: lactic acid as a solubilizing agent, hydrochloric acid for pH adjustment

Revised October 2008
This Medication Guide has been approved by the U.S. Food and Drug Administration.
Manufactured by:
Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Distributed by:
Schering-Plough
Schering Corporation
Kenilworth, NJ 07033
CIPRO is a registered trademark of Bayer Aktiengesellschaft and is used under license by Schering Corporation.
Rx Only
81532304, R.010/08 Bay o 9867 5202-2-A-U.S.-2614210
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CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy
CIPRO (ciprofloxacin HCl) Tablets Made in Germany

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Medication Guide only REMS Review

NDA:	NDA 19-537/S-070 NDA 19-847/S-044 NDA 19-857/S-051 NDA 20-780/S-028 NDA 21-473/S-025
Submission Date:	November 3, 2008
Drug Product:	CIPRO® (ciprofloxacin hydrochloride)Tablets CIPRO®IV (ciprofloxacin) 1% Solution in Vials CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose CIPRO® (ciprofloxacin) Oral Suspension CIPRO®XR (ciprofloxacin extended-release tablets)
Sponsor:	Bayer HealthCare Pharmaceutical, Inc.
Submission Type:	SLR/REMS
Deputy Director for Safety:	Ozlem Belen, MD, MPH
Division Director:	Renata Albrecht, MD
Safety Regulatory Project Manager:	Hyun Son, Pharm.D.
Drug Risk Management Analyst (OSE):	Doug Pham, Pharm.D., J.D.
DRISK Team Leader:	Jodi Duckhorn, MA

I. Background

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to make safety labeling changes (section 505 (o) (4) of the FDCA) and require the submission of a Risk Evaluation and Mitigation Strategy (REMS) (section 505-1(a)(2)) for an approved drug based upon new safety information that becomes available after the approval of the drug.

On July 7, 2008, DSPTP notified the Sponsors of all marketed fluoroquinolone antibiotics, including the Bayer HealthCare Pharmaceutical, that the current labeling did not adequately warn healthcare providers and patients about the increased risk of tendon-related adverse events. The Sponsor was advised of the required safety labeling changes, which include a Boxed Warning describing the increased risk for tendonitis and tendon rupture. In addition, the Sponsor was informed that REMS is necessary to ensure that the benefits of the drug outweigh the risks. The Sponsor was given 120 days to submit a REMS proposal.

The necessary elements of the REMS to be submitted included a Medication Guide (MG) and a timetable for assessment of the REMS. The professional labeling and the MG for CIPRO® and CIPRO®XR were approved on October 3, 2008.

- Proposed REMS for CIPRO® and CIPRO®XR were submitted on November 3, 2008.
- DSPTP sent a consult to the Division of Risk Management (DRISK) in OSE on November 12, 2008.
- DSPTP received the comments from the DRISK reviewer on January 16, 2009 and communicated these comments to Bayer on February 4, 2009.
- The Sponsor submitted revised REMS proposal on February 19, 2009 as requested.

- DRISK confirmed that the proposed REMS was acceptable via e-mail dated February 27, 2009 and requested that DSPTP remind the Sponsor to submit the patient surveys 60 days prior to conducting them.
- DSPTP also sent an email to the sponsor on March 13, 2009 to request removal of the sentence per compliance (see Reviewer's comment).
- On March 27, 2009, the sponsor submitted revised REMS as requested.

II. Materials Reviewed

1. Proposed REMS for CIPRO® and CIPRO® XR submitted by Bayer HealthCare Pharmaceutical, Inc. on November 3, 2008 and the revised REMS proposal submitted by the Sponsor dated February 19, 2009 and March 27, 2009.
2. DSPTP comments to the Sponsor dated February 4, 2009.
3. OSE/DRISK review of the proposed risk evaluation and mitigation strategy by Doug B. Pham, Pharm.D, J.D., Drug Risk Management Analyst, Jody Duckhorn, MA, Team Leader, Patient Labeling and Education dated January 16, 2009.
4. E-mail from Doug B. Pham, Pharm.D, J.D. of DRISK evaluating the revised REMS proposal submitted by the Sponsor dated February 19, 2009.

III. Summary of Recommendations by DRISK Reviewer

The following comments regarding the proposed REMS for CIPRO® and CIPRO® XR include some of the recommendations that were provided by the DRISK reviewer:

1. The sponsor was recommended to change the REMS goal as follows and in unison with the entire fluoroquinolone antibiotic class:

   The goal of the REMS is to inform patients of the serious risks associated with the use of Cipro, particularly the increased risks of tendonitis and tendon rupture.

2. Approving [redacted] (b) (4) as a component of this Medication Guide only REMS was not recommended.

3. The sponsor is expected to submit a detailed description of methodology and the instruments used in the patient survey. A complete description of survey protocols is to be submitted to FDA 60 days prior to conducting surveys.

   This survey protocol submission should include, but is not limited to:
   a. Sample size and confidence interval associated with that sample size
   b. How the sample will be determined (selection criteria)
   c. The expected number of patients surveyed
   d. How the participants will be recruited
   e. How and how often the surveys will be administered
   f. Explain controls used to minimize bias
   g. Explain controls used to compensate for the limitations associated with their methodology

h. The Sponsor should submit the survey instruments (questionnaires and moderator's guide) for review.
i. Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.

In addition, DSPTP is to incorporate the following language regarding the information needed to assess the effectiveness of the REMS into the approval letter:

a. *A survey of patients' understanding of the serious risks associated with any fluoroquinolone antibiotic*
b. *A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24*
c. *A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance*

IV. Reviewer's Comment:

The Office of compliance has reminded DSPTP that when a 60 day interval for sponsor to submit their REMS assessment which can create enforcement problems since the assessments would be expected within 2 months prior to the 18 months or 2 months afterwards. Therefore the following sentence was removed from the proposed REMS. DRISK reviewer was notified of this change.

(b) (4)

V. Recommendation

The approval letter was reviewed, revised and cleared by the Safety Requirements Team on March 10, 2009. An approval letter for the REMS should be sent to the sponsor (see approved REMS in the appendix below).

Appendix

NDA 19-847, NDA 19-857, NDA 20-780, NDA 19-537, NDA 21-473
Cipro® (ciprofloxacin)
Tablets, Oral Suspension, I.V. Solution, Extended Release Tablets
Class of Product: Fluoroquinolones
Bayer Healthcare Pharmaceuticals Inc.
P.O. Box 1000
Montville, NJ 07045-1000
1-888-842-2937

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

The goal of the REMS is to inform patients of the serious risks associated with the use of Cipro, particularly the increased risks of tendonitis and tendon rupture.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide (MG) will be dispensed with each Cipro® prescription.

> Pursuant to 21 CFR 208.24, the MG will be made available in sufficient numbers to US Cipro® distributors. US distributors will provide the MG with every pharmacy shelf carton of Cipro® to ensure its availability for dispensing to patients who are dispensed Cipro®. The label of each container or package of Cipro® will include a prominent instruction to authorized dispensers to provide a MG to each patient to whom the drug is dispensed, and state how the MG is provided.

B. Communication Plan

The REMS for Cipro does not include a Communication Plan.

C. Elements to Assure Safe Use

The REMS for Cipro does not include Elements to Assure Safe Use.

D. Implementation System

Because this REMS for Cipro does not include Elements to Assure Safe Use, an implementation system is not required.

III. Timetable for Submission of Assessment of REMS

Results that have become available from the individual assessment activities as well as corrective actions and other pertinent information will be summarized in REMS Assessment Reports that will be submitted to FDA at 18 months, 3 years, and 7 years after the REMS is approved.

_____

Hyun J. Son, Pharm.D.
Acting Safety Regulatory Project Manager

_____

Ozlem Belen, MD, MPH
Deputy Director for Safety

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/s/

Hyun Son
4/27/2009 02:53:35 PM
CSO

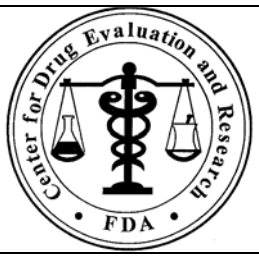
Ozlem Belen
4/27/2009 02:58:44 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

OTHER REVIEW(S)

	**Department of Health and Human Services** **Public Health Service** **Food and Drug Administration** **Center for Drug Evaluation and Research** **Office of Surveillance and Epidemiology**
Date:	January 16, 2009
To:	Renata Albrecht, M.D., Director Division of Special Pathogens and Transplant Products
Through:	Claudia Karwoski, Pharm.D, Director (Acting) Division of Risk Management (DRISK)
From:	**Scientific Lead:** Doug B. Pham, Pharm.D, J.D., Drug Risk Management Analyst (DRISK) Brian Gordon, MA, Social Science Reviewer (DRISK) Jodi Duckhorn, MA, Team Leader, Patient Labeling and Education (DRISK)
Subject:	Review of the Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Names:	Cipro® (ciprofloxacin) I.V. Solution Cipro® (ciprofloxacin) I.V. solution in 5% Dextrose Cipro® (ciprofloxacin) Oral Suspension Cipro® (ciprofloxacin hydrochloride) Tablets Cipro® XR (ciprofloxacin extended release tablets)
Application Type/Number:	NDA 19-847/SLR-044 NDA 19-857/SLR-051 NDA 20-780/SLR-028 NDA 19-537/SLR-070 NDA 21-473/SLR-025
Applicant/sponsor:	Bayer HealthCare Pharmaceutical, Inc.
OSE RCM #:	2008-1801

1 INTRODUCTION AND BACKGROUND

This review follows a request from the Division of Special Pathogen and Transplant Products (DSPTP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation Mitigation Strategy (REMS) of the following:

Bayer HealthCare Pharmaceutical, Inc.	NDA 19-847 Cipro® I.V. Solution NDA 19-857 Cipro® I.V. Solution in 5% Dextrose NDA 20-780 Cipro® Oral Suspension NDA 19-537 Cipro® Tablets NDA 21-473 Cipro® XR Tabets
Generic Sponsors	ANDA 76-126 ciprofloxacin (Carlsbad) ANDA 76-484 ciprofloxacin I.V. (Abraxis Pharm) ANDA 76-558 ciprofloxacin (Hikma) ANDA 76-992 ciprofloxacin I.V. (Bedford Labs) ANDA 76-993 ciprofloxacin I.V. (Bedford Labs) ANDA 77-245 ciprofloxacin I.V. (Hospira) ANDA 77-782 ciprofloxacin I.V. (Teva Parenteral) ANDA 78-062 ciprofloxacin I.V. (Clara Lifesciences)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to make safety labeling changes (section 505 (o) (4) of the FDCA) and require the submission of a Risk Evaluation and Mitigation Strategy (REMS) (section 505-1(a)(2)) for an approved drug based upon new safety information that becomes available after the approval of the drug.

On July 7, 2008, DSPTP notified the Sponsors of all marketed fluoroquinolone antibiotics, including the Sponsor Bayer HealthCare Pharmaceutical, that the current labeling did not adequately warn healthcare providers and patients about the increased risk of tendon-related adverse events. The Sponsor was advised of the required safety labeling changes, which include a boxed warning describing the increased risk for tendonitis and tendon rupture. In addition, the Sponsor was informed that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. The Sponsor was given 120 days to submit a REMS proposal.

The necessary elements of the REMS to be submitted included a Medication Guide (MG) and a timetable for assessment of the REMS. The professional labeling and the MG for all Cipro® NDAs (noted above) were approved on October 3, 2008.

ANDA sponsors (noted above) received notification requiring them to implement labeling changes recently approved to corresponding reference listed drugs. These sponsors are only required to adhere to professional labeling changes and Medication Guide requirements. A timetable for assessment of the REMS is not required by ANDA sponsors.

2 MATERIAL REVIEWED

- Proposed REMS for Cipro® (NDAs 19-537, 20-780, 19-847, 19-857, 21-473) dated November 3, 2008.

- Arnwine, K., Mills, S. Label and Labeling Review (Levaquin, Cipro, Avelox, Floxin, Noroxin, and Cellcept), dated December 12, 2008.

.

3 PROPOSED REMS

3.1 Goal

The Sponsor has proposed the following REMS goal:

> *The overall goals of the REMS are as follows:*
>
> *a.* (b) (4)
>
> *b. Improve patient awareness of the key safety factors concerning fluoroquinolone antimicrobials and ciprofloxacin in particular.*
>
> *The REMS has two objectives to help meet the above goals by using the Medication Guide (MedGuide):*
>
> *A.* (b) (4)
>
> *B. Assess patient understanding of safety information, as indicated in the ciprofloxacin MedGuide, over time*

The primary purpose for requiring a REMS is to communicate the serious risks associated with fluoroquinolone antibiotics, specifically tendonitis and tendon rupture, through the use of a Medication Guide (MG). The sponsor has proposed an adequate goal but has misappropriated the focus of the MG to both the patient (b) (4). MGs are primarily targeted towards the patient.

We suggest applying a generalized REMS goal to unify the fluoroquinolone antibiotic class. We recommend the following goal:

> *The goal of the REMS is to inform patients of the serious risks associated with the use of Cipro, particularly the increased risks of tendonitis and tendon rupture.*

3.2 REMS Elements

The REMS includes a Medication Guide and a timetable for assessment with the information needed for assessment. Each element is described below and a formatted REMS proposal is presented in Appendix A.

3.2.1 Medication Guide

A Medication Guide (MG) was approved for all marketed fluoroquinolone antibiotics on October 3, 2008, including one specific to Cipro. A MG will be provided to every patient who receives a prescription for Cipro.

Pursuant to 21 CFR 208.24, the sponsor will supply all U.S. distributors of Cipro with an adequate supply of MGs to accompany each pharmacy shelf carton for distribution. The label of each container or packaging of Cipro will provide prominent instruction for dispensing a MG with each prescription.

A review by the Division of Medication Error Prevention and Analysis (DMEPA) in OSE was conducted on December 12, 2008 to assess current labeling compliance with 21 CFR 208.24(d)[1]. The labeling on the carton/container was found not to be in accordance with 21 CFR 208.24(d) and a number of revisions were suggested in the review. DSPTP issued comments to the Sponsor on December 19, 2008 and currently awaiting a response.

If the Sponsor accepts the proposed carton/container labeling modifications, then the Sponsor's proposal for MG distribution is compliant with 21 CFR 208.24 and is acceptable.

3.2.2 Communication Plan

A communication plan is not required as a component of the proposed REMS.

3.2.3 Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use.

3.2.4 Timetable for Assessment of the REMS

The sponsor will submit a REMS Assessment to FDA at 18 months, 3 years, and 7 years following REMS approval. The sponsor will submit assessments within 60 days of the noted time intervals.

[1] Arnwine, K., Mills, S. Label and Labeling Review (Levaquin, Cipro, Avelox, Floxin, Noroxin, and Cellcept), dated December 12, 2008.

Information needed for assessment is not a required element of the REMS Proposal. However, this information should be addressed in the REMS approval letter and discussed in the REMS supporting documents.

Information needed for assessment will include but is not be limited to:

c. A survey of patients' understanding of the serious risks associated with any fluoroquinolone antibiotic
d. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
e. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The sponsor has provided brief synopses of their proposed patient (b) (4) survey protocols, as well as a description for assessing the distribution and dispensing of the MG within their REMS supporting documents.

The target dates for submitting the survey reports are described in the above assessment timetables. Each survey type is discussed below.

A. Patient Survey

The Sponsor proposes to conduct a patient survey to assess the patient's understanding of the risks associated with Cipro. The patient survey will be conducted via the internet. The survey will contain questions about receiving the Medication Guide, the risks associated with Cipro (tendon disorders, QT prolongation and hypersensitivity reactions), and what to do if you experience these side effects.

The proposed patient survey does not provide adequate detail in methodology to conduct a complete assessment. We recommend the Sponsor submit a complete description of methodology and the instruments used to measure patient's understanding of the risks and safe use of Cipro to FDA 60 days prior to conducting the survey. This submission should include, but is not limited to:

- Sample size and confidence interval associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of patients surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with their methodology
- The Sponsor should submit the survey instruments (questionnaires and moderator's guide) for review.

- Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.

(b) (4)

[redacted]

[redacted]

4 CONCLUSION AND RECOMMENDATIONS

The Division of Risk Management in the Office of Surveillance and Epidemiology propose the following comments and recommendations regarding the proposed REMS for Cipro® (ciprofloxacin) oral tablets, oral suspension, extended release, and I.V. formulations:

1. Please see appended REMS proposal for additional track changes corresponding to comments in this review.
2. We recommend that the sponsor change the REMS goal as noted above to unify the entire fluoroquinolone antibiotic class.
3. If the Sponsor accepts suggested carton/container labeling recommendations (noted in DMEPA's review), we find the proposal for MG distribution acceptable.
4. We recommend DSPTP incorporate the following language regarding the information needed to assess the effectiveness of the REMS into the approval letter.
    a. A survey of patients' understanding of the serious risks associated with any fluoroquinolone antibiotic
    b. A report on periodic assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
    c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
5. We do not recommend approving (b) (4) as a component of this Medication Guide only REMS.
6. We recommend the Sponsor submit a detailed description of methodology and the instruments used in the patient survey. This submission should include, but is not limited to:
    a. Sample size and confidence interval associated with that sample size
    b. How the sample will be determined (selection criteria)
    c. The expected number of patients surveyed
    d. How the participants will be recruited

e. How and how often the surveys will be administered
f. Explain controls used to minimize bias
g. Explain controls used to compensate for the limitations associated with their methodology
h. The Sponsor should submit the survey instruments (questionnaires and moderator's guide) for review.
i. Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.

7. We recommend the Sponsor submit a complete description of survey protocols to FDA 60 days prior to conducting surveys.

APPENDIX A: CIPRO REMS

NDA 19-847, NDA 19-857, NDA 20-780, NDA 19-537, NDA 21-473
Cipro® (ciprofloxacin)
Tablets, Oral Suspension, I.V. Solution, Extended Release Tablets

Class of Product: Fluoroquinolones

Bayer Healthcare Pharmaceuticals
P.O. Box 1000
Montville, NJ 07045-1000
[Insert contact information]

(b) (4)

(b) (4)

(b) (4)

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

(b) (4)

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Mary Dempsey
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DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
1/16/2009 03:14:47 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S-070

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: February 5, 2009

To: Janet Herrington	**From:** Hyun Son, Pharm.D.
Company: Bayer	Division of Special Pathogens and Transplant Products
Fax number: Email	**Fax number:** 301-796-9881
Phone number:	**Phone number:** 301-796-1939

Subject: Cipro and Cipro XR: REMS Comments

Total no. of pages including cover: 5

Concurrence:

Ozlem Belen, MD, MPH Safety Deputy Director

Document to be mailed: ❑ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Please refer to your November 3, 2008 submissions consisting of the Risk Evaluation and Mitigation Strategy (REMS) proposal for Cipro and Cipro XR. We have reviewed the submissions and have the following comments:

1. Please submit your REMS proposal with additional track changes as noted below in the attachment.

2. We recommend that you change the REMS goal as noted below to unify the entire fluoroquinolone antibiotic class.

3. We do not recommend incorporating (b) (4) as a component of this Medication Guide only REMS. In Medication Guide (MG) only REMS, the assessment of the REMS should evaluate the effectiveness of the MG as an educational tool to inform patients, assess if patients are receiving the Medication Guide, and assess patient understanding of the risks associated with the product.

4. The REMS supporting documents need to be consistent with the updated REMS.

Please provide the requested changes above by February 18, 2009.

We recommend you submit a complete description of survey protocols to FDA 60 days prior to conducting the survey. The goal of the survey is patient's understanding of the serious risks, particularly the increased risks of tendonitis and tendon rupture.

This submission should be a detailed description of methodology and the instruments used in the patient survey. This survey protocol submission should include, but is not limited to:

a) Sample size and confidence interval associated with that sample size
b) How the sample will be determined (selection criteria)
c) The expected number of patients surveyed
d) How the participants will be recruited
e) How and how often the surveys will be administered
f) Explain controls used to minimize bias
g) Explain controls used to compensate for the limitations associated with their methodology
h) The Sponsor should submit the survey instruments (questionnaires and moderator's guide) for review.
i) Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.

We are providing the above information by email for your convenience. Contact me at 301-796-1939 if you have any questions regarding the contents of this transmission. Thank you.

Hyun Son, Pharm.D.
Acting Safety Regulatory Project Manager

APPENDIX A: CIPRO REMS

NDA 19-847, NDA 19-857, NDA 20-780, NDA 19-537, NDA 21-473
Cipro® (ciprofloxacin)
Tablets, Oral Suspension, I.V. Solution, Extended Release Tablets
Class of Product: Fluoroquinolones
Bayer Healthcare Pharmaceuticals
P.O. Box 1000
Montville, NJ 07045-1000
[Insert contact information]

(b) (4)

[redacted]

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

(b) (4)

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Hyun Son
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CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-537/S-070 and S-071
NDA 19-847/S-044 and S-045
NDA 19-857/S-051 and S-052
NDA 20-780/S-028 and S-029
NDA 21-473/S-025 and S-026

PRIOR APPROVAL SUPPLEMENTS

Bayer Pharmaceuticals Corporation
Attention: Janet Herrington, Ph.D.
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, New Jersey 07045-1000

Dear Dr. Herrington:

Please refer to your New Drug Applications (NDAs) for CIPRO® (ciprofloxacin).

A. Acknowledgement of Label Supplements

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Drug Product Name	NDA Number	Supplement number	Date of supplement	Date of receipt
CIPRO® (ciprofloxacin hydrochloride) Tablets	19-537	S-071	November 3, 2008	November 3, 2008
CIPRO® IV (ciprofloxacin) 1% Solution in Vials	19-847	S-045	November 3, 2008	November 14, 2008
CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose	19-857	S-052	November 3, 2008	November 14, 2008
CIPRO® (ciprofloxacin) Oral Suspension	20-780	S-029	November 3, 2008	November 14, 2008
CIPRO® XR (ciprofloxacin extended-release tablets)	21-473	S-026	November 3, 2008	November 14, 2008

These supplemental applications propose the following: updating the carton and container labels to include a statement to let dispensers know that a Medication Guide must be dispensed with the product, in compliance with the Medication Guide Regulations as specified in 21 CFR 208.24 (d).

B. Acknowledgement of REMS Supplements

We have also received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Drug Product Name	NDA Number	Supplement number	Date of supplement	Date of receipt
CIPRO® (ciprofloxacin hydrochloride) Tablets	19-537	S-070	November 3, 2008	November 3, 2008
CIPRO® IV (ciprofloxacin) 1% Solution in Vials	19-847	S-044	November 3, 2008	November 14, 2008
CIPRO® IV (ciprofloxacin) 0.2 % Solution in 5% Dextrose	19-857	S-051	November 3, 2008	November 14, 2008
CIPRO® (ciprofloxacin) Oral Suspension	20-780	S-028	November 3, 2008	November 14, 2008
CIPRO® XR (ciprofloxacin extended-release tablets)	21-473	S-025	November 3, 2008	November 14, 2008

These supplemental applications propose the following: your proposed Risk Evaluation and Mitigation Strategy (REMS) containing your approved Medication Guide.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on January 3, 2009 (NDA 19-537/S-070 and S-071) and January 14, 2009 (the remaining supplements) in accordance with 21 CFR 314.101(a).

Please cite the application numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

Kristen Miller, Pharm.D.
Safety Regulatory Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Kristen Miller

11/17/2008 04:32:24 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Surveillance and Epidemiology

FROM: Division of Special Pathogen and Transplant Products
Kristen Miller, Pharm.D., Safety Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 11, 2008	N/A	**Levo: 20-634, 20-635, 21-721** **Cipro: 19-537, 20-780,** **19-847, 19-857 & 21-473** **Moxi: 21-085, 21-277** **Proquin: 21-744** **Gemi: 21-158** **Norflox: 19-384**	REMS	November 3, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Levaquin, Cipro, Avelox Factive, Proquin, Noroxin	Priority	**4030100, Antibacterial-Quinolone**	December 5, 2008

NAME OF FIRM: Ortho McNeil/ J&J PRD (Levaquin); Oscient Pharmaceuticals (Factive); Bayer (Cipro, Avelox); Merck (Noroxin), DepoMed (Proquin)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ BIOAVAILABILTY STUDIES ☐ PHASE IV STUDIES	☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

During the week of November 3, 2008, sponsors of quinolone products submitted REMS supplements that contained only a Medication Guide in response to the REMS/SLR Requests issued on 7/7/08. The Medication Guides were approved on October 3, 2008. As these are Medication Guide-only REMS, there is a two month review time. We would appreciate your feedback on the assessments the sponsors have proposed. All of the submissions have been placed in the eRoom: http://eroom.fda.gov/eRoom/CDER/CDER-DSPIDPL/0_80320.

Thank you for your assistance with our review. Please let Ozlem Belen or me (until November 17) or Hyun Son (acting Safety Project Manager beginning November 17) know if you have any questions regarding this request. Thank you very much!

SIGNATURE OF REQUESTER Kristen Miller, Pharm.D.	METHOD OF DELIVERY (Check one) ■ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kristen Miller

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