



NDA 21-061/S-023, S-024  
NDA 21-062/S-026, S-037

Bristol Myers-Squibb Company  
Attention: Amy A. Jennings, Ph.D.  
Senior Regulatory Associate, Global Regulatory Sciences  
5 Research Parkway  
P.O. Box 5100  
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your supplemental new drug applications, which were submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA #	Drug Product	Supplement Number	Letter Date	Receipt Date
21-061	Tequin <sup>®</sup> (gatifloxacin) Tablets, 200 mg and 400 mg	S-023	March 18, 2004	March 19, 2004
		S-024	March 29, 2004	March 30, 2004
21-062	Tequin <sup>®</sup> (gatifloxacin in 5% dextrose) Injection	S-026	March 18, 2004	March 19, 2004
		S-027	March 29, 2004	March 30, 2004

Please refer to your amendments dated March 29, 2004, and August 5, 2004 to NDA 21-061/S-023 and NDA 21-062/S-026. Please also refer to your amendments dated August 26, 2004 to NDA 21-061/S-023, S-024 and NDA 21-062/S-026, S-037.

NDA 21-061/S-023 (Tablets) and NDA 21-062/S-026 (Injection) were submitted as “Special Supplements- Changes Being Effected” (CBEs) and provide for the addition of quinolone class labeling as was requested in the Division’s supplement request letter on November 26, 2003 and the facsimiles from the Division dated March 10, and July 26, 2004. The **WARNINGS: QTc Interval Prolongation**, **WARNINGS: Tendon Effects**, **WARNINGS: Peripheral Neuropathy** and **PRECAUTIONS: Information for Patients** sections were revised.

NDA 21-061/S-024 (Tablets) and NDA 21-062/ S-027 (Injection) were submitted as “Special Supplements- Changes Being Effected” (CBEs) and provide for labeling changes to the **Patient Information About:** and **What are the possible side effects of TEQUIN?** sections of the patient package insert.

These supplements provide for the following changes to the Tequin<sup>®</sup> (gatifloxacin) Tablets, 200 mg and 400 mg and Tequin<sup>®</sup> (gatifloxacin) Injection, 200 mg and 400 mg label. Deleted text is noted by ~~strikethrough~~ and added text is noted by double underline:

1. The following revisions were made under the **WARNINGS** section:

~~Prolongation of the QTc Interval~~

~~**GATIFLOXACIN HAS THE POTENTIAL TO PROLONG THE QTc INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. DUE TO THE LACK OF CLINICAL EXPERIENCE IN PATIENTS WITH KNOWN PROLONGATION OF THE QTc INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA, AND PATIENTS RECEIVING CLASS IA (EG, QUINIDINE, PROCAINAMIDE) OR CLASS III (EG, AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS, GATIFLOXACIN SHOULD BE AVOIDED IN THESE PATIENT POPULATIONS.**~~

**QTc Interval Prolongation**

Gatifloxacin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. Rare cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving quinolones, including gatifloxacin. Nearly all of these rare cases were associated with one or more of the following factors: age over 60, female gender, underlying cardiac disease, and/or use of multiple medications. No cardiovascular morbidity or mortality attributable to QTc prolongation has occurred in over 44,000 patients treated with gatifloxacin in clinical trials; these include 118 patients concurrently receiving drugs known to prolong the QTc interval and 139 patients known to have uncorrected hypokalemia (ECG monitoring was not performed). Gatifloxacin should be avoided in patients with known prolongation of the QTc interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. (See **CLINICAL PHARMACOLOGY: Electrocardiogram.**)

Pharmacokinetic and pharmacodynamic studies between gatifloxacin and drugs that prolong the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gatifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia.

The magnitude of QTc prolongation increases with increasing concentrations of the drug;~~QTc prolongation may lead to an increased risk for ventricular arrhythmias including~~

~~torsades de pointes~~—(see **CLINICAL PHARMACOLOGY: Electrocardiogram**); therefore, the recommended dose and the recommended intravenous infusion rate should not be exceeded (see **DOSAGE AND ADMINISTRATION** for dosing recommendations for patients with or without renal impairment).

~~No cardiovascular morbidity or mortality attributable to QTc prolongation has occurred in over 44,000 patients treated with gatifloxacin in clinical trials; these include 118 patients concurrently receiving drugs known to prolong the QTc interval and 139 patients known to have uncorrected hypokalemia (ECG monitoring was not performed). During postmarketing surveillance, rare cases of torsades de pointes have been reported in patients taking gatifloxacin. These cases have occurred primarily in elderly patients with underlying medical problems for which they were receiving concomitant medications known to prolong the QTc interval; the contribution, if any, of gatifloxacin to the development of torsades de pointes in these patients is unknown.~~

### **Tendon Effects**

Ruptures of the shoulder, hand, and Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including gatifloxacin. Postmarketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Gatifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including gatifloxacin.

~~Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. TEQUIN should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones.~~

### **Peripheral Neuropathy**

Rare 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 quinolones.

2. The following revisions were made under the **PRECAUTIONS** section, **Information for Patients** subsection:

- that TEQUIN may ~~produce~~cause changes in the electrocardiogram (QTc interval prolongation);
- that TEQUIN should be avoided in patients receiving ~~Class~~class IA (eg, quinidine, procainamide) or ~~Class~~class III (eg, amiodarone, sotalol) antiarrhythmic agents;
- that TEQUIN should be used with caution in ~~patients~~subjects receiving drugs that ~~may effect~~affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants;
- to inform their physicians of any personal or family history of QTc prolongation or proarrhythmic conditions such as ~~recent~~ hypokalemia, ~~significant~~ bradycardia, or recent myocardial ischemia;
- to discontinue treatment and contact their physician if symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop;

3. The following typographical error was made in the patient package insert and will be corrected in the final printed labeling:

**Patient Information About:**

**TEQUIN<sup>®</sup>**

**(gatifloxacin)**

**200 mg and 400 mg Tablets**

4. The following revisions were made in the patient package insert, under the

**What are the possible side effects of TEQUIN?** section, second paragraph:

In a few people, TEQUIN, like some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. Although this ~~has not caused~~did not cause any problems in ~~more than 4000~~ patients who ~~have taken~~took TEQUIN in premarketing clinical trials, in theory, it could result in extremely rare cases of abnormal heartbeat, which may be dangerous. Contact your healthcare professional if you develop heart palpitations (fast beating) or have fainting spells.

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug

product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 26, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated **“FPL for approved supplement NDA 21-061/S-023, S-024 and NDA 21-062/S-026, S-027.”** Approval of this submission by FDA is not required before the labeling is used.

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

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Christine Lincoln, Labeling Reviewer, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Immunologic  
Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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Renata Albrecht  
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