

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-678

MEDICAL REVIEW(S)

NDA 21-678, gatifloxacin for oral suspension

**Division Director Review -
Gatifloxacin for Oral Suspension**

Drug Name Established: Gatifloxacin

Proprietary: Tequin®

Route: Oral

Application: NDA 21-678, gatifloxacin for oral suspension

Related NDA's: NDA 21-061, gatifloxacin tablets
NDA 21-062, gatifloxacin in 5% dextrose injection
(administrative NDAs 21-404 and 21-405 for skin indication)

Date of Submissions: October 27, 2003

PDUFA Goal Date: August 27, 2004

Applicant: Bristol Myers-Squibb Pharmaceutical Research Institute
Five Research Parkway
Wallingford, Connecticut 06492

Subject: APPROVAL OF gatifloxacin for oral suspension

Synopsis:

This review summarizes data on a new formulation of gatifloxacin – gatifloxacin for oral suspension – for use in adult patients for the same indications as currently approved for the gatifloxacin tablet and IV formulations.

Finally, labeling recommendations, including input from OCTAP/DPDD is summarized.

RECOMMENDATIONS:

(1) Approval

This NDA should be approved. The applicant has demonstrated that NDA 21-678, Tequin® (gatifloxacin) for Oral Suspension is bioequivalent to the approved Tequin® (gatifloxacin) Tablets and has updated the labeling to reflect this information, and added new information on arthrototoxicity in the ANIMAL PHARMACOLOGY section of the labeling. The CMC and inspection information is satisfactory.

(2) Post marketing commitments

There are no post-marketing commitments (—)
Although this product is not being approved for pediatric use, it is possible HCPs may use the suspension formulation off label in such a population. The company has stated that they will voluntarily evaluate any post-marketing events that may be reported in pediatric patients.

(3) Pediatric drug development

(a) Pediatric Research Equity Act (PREA)

Given the history of drug development with fluoroquinolones, the specific scientific and regulatory issues of pediatric drug development of gatifloxacin, and the fact that some indications were waived in the 1999 approval letter for the tablets and IV formulations, the question of which indications could be appropriately waived or deferred was consulted to OCTAP/DPDD. Their advice is summarized below:

Under PREA, the criteria for waiving pediatric studies are as follows:

- 1) The necessary studies are impossible or highly impractical;
- 2) There is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups; or
- 3) The drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

We believe that for some of the approved indications, gatifloxacin does not meet these criteria for the waiver. There was an AC held in 1997 which recommended that the quinolones only be studied in pediatric patients for serious infections. Our division thinks that gatifloxacin may meet these criteria for several indications. However, more safety data would be needed before initiating pediatric studies.

Therefore, we recommend that you **waive** pediatric studies for the following indications:

- acute sinusitis
- uncomplicated urinary tract infections
- uncomplicated skin and skin structure infections, and acute exacerbations of chronic bronchitis.

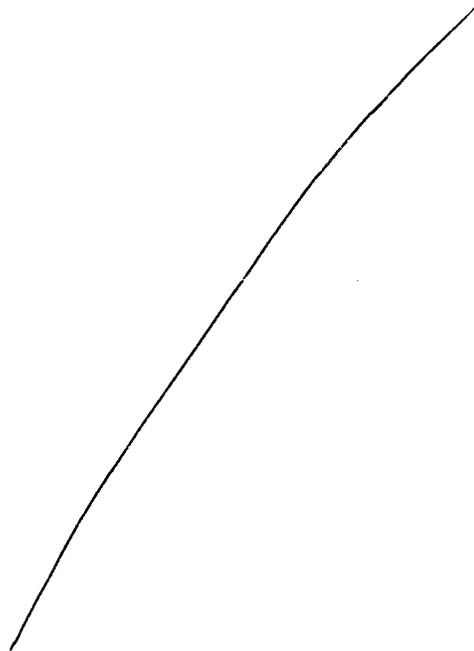
We recommend that you **defer** pediatric studies for the following serious infections until more safety data for gatifloxacin is collected:

- community acquired pneumonia
- complicated urinary tract infections including pyelonephritis
- uncomplicated u — gonorrhea in post-pubertal males : —

This advice is in line with the divisions and the applicant will be informed that complicated urinary tract infections and community acquired pneumonia are deferred.

Studies of uncomplicated gonorrhea are considered fulfilled from an efficacy perspective because the data in adult patients can be extrapolated to adolescent patients. The disease is infrequent and not practical to study in younger patients, therefore studies in prepubescent and premenarchal patients should be waived. However, because of the pre-clinical findings of arthrotoxicity in fluoroquinolones including gatifloxacin, and the absence of safety data in the adolescent age group, no revision in labeling to extend the indication to the adolescent age group is proposed at this time. Gonorrhea is treated with a single dose of gatifloxacin. Therefore, safety data could be obtained in studies of gonorrhea in adolescent patients, to support the use of a single dose in adolescent patients with this infection.

Studies of acute exacerbation of chronic bronchitis are waived because this infection is not relevant to pediatric patients. Studies of uncomplicated urinary tract infections, uncomplicated skin and skin structure infections and acute bacterial sinusitis are waived because the potential risk may outweigh the potential benefit for these indications.



BACKGROUND:

Gatifloxacin Tablets and Injection were originally approved December 27, 1999 for the following indications:

NDA 21-678, gatifloxacin for oral suspension

- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis
- Acute sinusitis
- Uncomplicated urinary tract infections
- Complicated urinary tract infections including pyelonephritis
- Uncomplicated urethral, pharyngeal and rectal gonorrhea in males and uncomplicated endocervical, pharyngeal and rectal gonorrhea in females

At the same time, the drug received an approvable action for the indication of Uncomplicated skin and skin structure infections, and the company was asked for additional safety data both from an active surveillance trial, from post marketing and from studies of QT effects. This indication was approved October 17, 2002 and the labeling was revised to include new WARNING information about symptomatic hyperglycemia and hypoglycemia, particularly in patients who were elderly and/or had diabetes mellitus. The product labeling also includes WARNINGS on QT prolongation, CNS adverse events, hypersensitivity reactions, pseudomembranous colitis and tendon rupture. The most commonly reported adverse events in the clinical studies submitted to the NDA were nausea, vaginitis, diarrhea, headache and dizziness.

The original approval letter also stated that pediatric studies were waived for the originally-approved indications. This decision was based on the WARNING regarding arthrototoxicity of fluoroquinolones in juvenile animals. In the 1997 advisory committee meeting, the committee recommended that fluoroquinolones could be studied in serious infections.

Therefore, the applicant should evaluate gatifloxacin for complicated urinary tract infections and community acquired pneumonia in patients 0-18 years of age, and uncomplicated gonorrhea in postpubertal patients. The other indications, acute sinusitis, uncomplicated urinary tract infections, uncomplicated skin and skin structure infections are waived because the potential benefit does not outweigh the potential risk. Studies of acute exacerbation of chronic bronchitis are waived because this infection is not relevant to pediatric patients.

NDA FOR GATIFLOXACIN FOR ORAL SUSPENSION:

The gatifloxacin for oral suspension NDA was submitted October 27, 2003, and requested approval for

- (1) Adult patients for the same indications that are currently approved for the tablet. The basis for this request was the bioequivalence between the oral suspension formulation and the tablet formulation.

Review of the NDA for Adult Indications:

Based on the biopharmaceutics review, the oral suspension is bioequivalent to the tablet. This information is reflected in the CLINICAL PHARMACOLOGY section of the labeling. The CMC and inspection information is satisfactory. Therefore, the application can be approved for adults and there are no outstanding issues as far as approval for adults.

Labeling, including consideration for including pediatric information in labeling:

Final labeling was negotiated with the company following input from the Division and other groups including ODS/DMETS, DDMAC and OCTAP/DPDD.

OCTAP/DPDD recommended that the labeling should include the results of the preclinical study that provided information on the persistence of the histologic changes seen in juvenile dogs during the recovery period in this 6 months study. Satisfactory wording on this issue was negotiated with BMS and agreed on August 25, 2004.

This additional juvenile dog study that was conducted using 3 different doses (5 mg/kg, 10 mg/kg, 20 mg/kg) and a control. Animals were dosed for 14 days, half were sacrificed and examined after treatment and half were followed for a total of 6 month recovery phase. The results of this trial showed that there were no drug related effects at the 5 mg/kg dose. At 10 mg/kg/day and 20 mg/kg/day, dose related changes in cartilage and growth plate were seen. In addition, animals had clinical abnormalities (e.g., joint hyperextension) starting at week 3 and recovering between weeks 19-26 after treatment. At the end of recovery, there were no clinical abnormalities, growth plate abnormalities resolved, but some animals had persistence of cartilage erosion and fissures on histologic examination. This information will be included in the labeling.

In an additional study immature dogs given gatifloxacin orally for 2 weeks with a 6-month recovery period, articular cartilage lesions were observed at > 5 mg/kg (approximately 0.3 times human therapeutic dose levels based on plasma AUC comparisons), and growth plate cartilage lesions were seen at 10 and 20 mg/kg (approximately equivalent to human therapeutic dose levels based on plasma AUC comparisons). Articular cartilage changes seen on gross pathology and histopathology persisted through the 6-month recovery period, whereas growth plate cartilage lesions were resolved. (See WARNINGS). The relevance of these findings to the clinical use of gatifloxacin is unknown.

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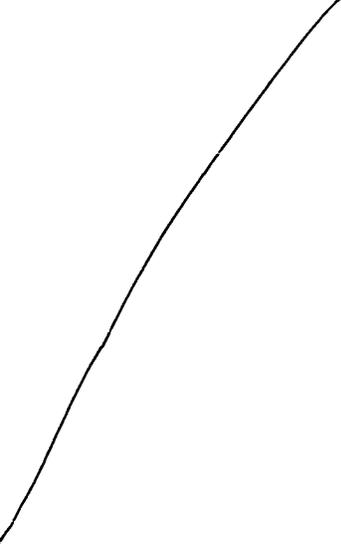
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MEDICAL OFFICER

**DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG
PRODUCTS (HFD-590)**

NDA 21-678: Gatifloxacin Powder for Oral Suspension



the Division completed the review of the powder for oral suspension (POS) to ensure safety and demonstration of bioequivalence (BE) to the approved intravenous and tablet formulations. Please refer to the Biopharmaceutical review of NDA 21-678 for details of the BE review of gatifloxacin POS.



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