# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-334 *and* 21-085/S-010**

# MEDICAL REVIEW

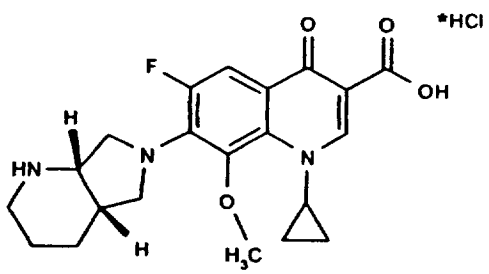
**Medical Officer Review of NDA 21-334:**
**Avelox® for the treatment of uncomplicated skin and soft structure infections.**

| | |
|---|---|
| Date Submitted: | 28 September 2000 |
| Date Received: | 29 September 2000 |
| Date Assigned: | 17 January 2001 |
| Date Completed: | 27 April 2001 |

**Applicant:** Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, Connecticut 06516
Contact: Mr Andrew Verderame, Associate Director, Regulatory Affairs
Phone: 203-812-5172

Drug:

| | |
|---|---|
| Proprietary name: | Avelox® |
| Generic name: | Moxifloxacin (BAY 12-8039) |
| Chemical name: | 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid |
| Molecular formula: | $C_{21}H_{24}FN_3O_4$ *HCl |
| Molecular weight: | 437.9 daltons |
| Molecular structure: | |




Drug class: Antimicrobial-fluoroquinolone
Formulation: 400 mg capsules
Route of Administration: Oral
Related NDAs:
21-085/S-010

Related INDs:

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# Executive Summary

## *Background*

The Bayer Company submitted an application (NDA 21-085) on December 9, 1998, for the following indications:

- Community acquired pneumonia (CAP)
- Acute bacterial exacerbation of chronic bronchitis (ABECB)
- Acute maxillary sinusitis
- Uncomplicated skin and skin structure (USSI)

The data submitted in that application allowed for an approval of the first three indications on December 10, 1999. However, they received an approvable decision for the fourth: treatment of uncomplicated skin and skin structure infections. The reason for the approvable decision was secondary to concerns about the risk benefit profile for this indication. Specifically, the Division had concerns about moxifloxacin's effect on cardiac repolarization, which can be clinically detected as a prolongation of the QT interval on a patient's electrocardiogram. As is well known, excessive prolongation of this interval can result in life-threatening cardiac dysrhythmias.

In order for the USSI indication to be considered, Bayer was asked to perform several studies, which they agreed to be Phase IV commitments. These commitments are further described in the section entitled **Regulatory Background** of this document. The submission dated 28 September 2000 consists of resubmission of the efficacy data for the USSI indication, as well as the results Phase IV studies. This submission has been given a new NDA number, 21-334, for administrative purposes.

This medical officer review will comment on the data submitted for three of the Phase IV commitments:

1. Submission of the results of an active surveillance program in the United States, providing information on the incidence of adverse events for at least 15,000 moxifloxacin exposures.
2. Submission of the results of the active surveillance program that was underway in Germany at the time that the previous action was taken (December 1998). This report was to include information on the incidence of adverse events for at least 15,000 moxifloxacin exposures.
3. Submission of post-marketing adverse event data following use in at least one million patients worldwide. This report incorporated data from the two active surveillance studies described above.

## *Results*

*Cardiac Toxicity*

While all three reports had deficiencies it was still possible to evaluate the results with respect to the incidence of life-threatening cardiac arrhythmias.

The US-based active surveillance study did not document a high rate of malignant ventricular arrhythmias. This finding corroborated the observations made in the original NDA database of approximately 5000 patients. However, it must be noted that further

characterization of the cardiac safety of moxifloxacin is limited in this study because the majority of the patients who experienced potential cardiac-related adverse events did not have electrocardiograms performed.

The active surveillance study in Germany was well underway in December 1999 (on the 3rd month of an 8 month study), therefore it was not possible to make substantial comments and recommendations regarding the study design and conduct. Although the amount of electrocardiographic data that was available from this study was sub-optimal, the study did not identify malignant cardiac events in 16,000 treated subjects.

The one million patient study incorporated the information from the above studies, plus worldwide spontaneous adverse event reports for the period June 1999 to June 2000. Among the estimated 1,560,000 treated patients on record, there was one case of torsade de pointe reported in an 83 year-old woman with underlying heart disease. There were at least six other cases of adverse events that could have had a cardiac etiology, but since additional clinical information was not available, any attribution is speculative.

*Serious hypersensitivity/Anaphylaxis reaction*
Spontaneous safety reporting for moxifloxacin in the early post-marketing period suggested that there were a substantial number of reports of hypersensitivity reactions. These reactions were characterized by facial or laryngeal edema and/or hypotension.

The applicant submitted wording for the revision of the package insert on December 11, 2000 (NDA 21-085/S-010). It provided for:

- The addition of a Post-marketing Events Reports subsection in the **ADVERSE REACTIONS** section of the label, which would include information about anaphylactic reaction and anaphylactic shock.
- Revisions to the **Precautions, Information for Patients** section regarding information about hypersensitivity reactions (including anaphylactic reactions).

Systematic review of the issue included an analysis of the data from the active surveillance studies, consultations with OPDRA staff, and review of the medical literature.

Review of the data from the first year of marketing indicated that serious anaphylaxis reactions occurred at a rate of about 22 per million exposures. Review of the data from the active surveillance study demonstrated a rate of anaphylaxis of about 100 per million exposures, when laryngeal edema is used as the marker event. These early data suggest that the rate at which patients experience anaphylaxis following administration of moxifloxacin may approach what has been reported for penicillin: 40 to 150 events per million exposures.

[redacted]

### *Conclusions and Recommendations*

The applicant fulfilled all of the Phase IV requirements that were stipulated in the approval letter from December 1999. The data generated from these studies were able to expand the safety database of moxifloxacin, and demonstrated that there was no increased mortality associated when used according to the approved dosage and frequency of administration. The recommendation is for approval of moxifloxacin, 400 mg qd po for 7 days, for the treatment of uncomplicated skin and skin structure infections.



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ON ORIGINAL

# Introduction

## Regulatory Background

The submission of NDA 21-334 follows the approval of moxifloxacin (NDA 21-085, Avelox 400 mg tablet) on December 10, 1999 for community-acquired pneumonia (CAP), acute bacterial exacerbation of chronic bronchitis (ABECB), and acute maxillary sinusitis. The applicant had also requested approval for skin and skin structure infections. The review division determined that this indication was approvable pending the submission of post-marketing safety data demonstrating an acceptable risk-benefit profile. Moxifloxacin had been found to affect cardiac repolarization and prolong the QT interval of the electrocardiogram. At the time of the approval of NDA 21-085, a number of phase IV studies were requested to better characterize the safety profile of moxifloxacin. These are presented below in italics:

1. *To better understand the risk/benefit profile of oral moxifloxacin tablets, Bayer will review post-marketing adverse event data following at least one million patient exposures worldwide. A substantial proportion of these exposures will be from the United States. The results of this evaluation will be submitted to the Division by September 30, 2000.*

2. *Bayer will conduct and submit the results of its active surveillance program currently being conducted in Germany or other foreign countries where active surveillance programs currently exist. The results of this program will provide information on incidence of adverse events using moxifloxacin tablets for at least 15,000 moxifloxacin exposures. Please submit protocols and methods for this ongoing study to the Division within ninety days of receipt of this letter. A report on this experience will be submitted to the Division by September 30, 2000*

3. *Bayer will conduct and submit the results of an active surveillance program in the United States similar to the ongoing moxifloxacin active adverse event surveillance program in Germany. The results of this program should provide information on incidence of adverse events using moxifloxacin tablets for at least 15,000 moxifloxacin exposures. Before initiating this study, please submit the protocol and proposed methods within ninety days of receipt of this letter. The results of this study should be submitted to the Division by September 30, 2000.*

4. *Bayer will conduct a moxifloxacin single oral dose escalation study of the effects on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.*

5. *Bayer will conduct a comparison study of the effects of moxifloxacin, levofloxacin, and erythromycin on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.*

6. *Bayer will conduct a ten day multiple dose comparison study of moxifloxacin, sparfloxacin, and placebo effects on QTc at Cmax. The results of this study will be submitted to the Division by December 31, 2000.*

7. *Bayer will perform a study to characterize the pharmacokinetic profile of moxifloxacin and its conjugated metabolites (M1 and M2) in young and elderly adult males and females after single and multiple 400 mg oral doses. The results of this study will be submitted to the Division by December 31, 2000.*

8. *Bayer will re-evaluate the drug substance impurity specifications after 2 years of commercial production for the following three impurities:* [redacted]

NDA 21-334 is the resubmission of the efficacy data for skin and skin structure infections plus the results of phase IV studies numbered 1-7 above. As specified in the action letter of December 10, 1999, the safety data to support the approval of skin and skin structure infections are included in studies 1, 2, 4, 5, and 6.

Draft labeling submitted with NDA 21-334 includes a new statement for the Avelox tablet label that is based on the results of study 3. That statement is reproduced below:

*"In a US postmarketing observational study, monitoring the safety experience of AVELOX Tablets in more than 18,000 outpatients, no evidence of increased cardiovascular mortality or morbidity was observed with moxifloxacin treatment."*

## Clinical Studies

This application included data from the first seven of the eight phase IV studies listed above. Study #3 is reviewed below. The reader is referred to the following documents for the review of the remaining phase IV studies: Study No. 1) Medical Officer review of Dr. Leonard Sacks, No. 2) Medical Officer review of Dr. Eileen Navarro, Nos. 4-7) Clinical pharmacologist review of Dr. Joette Meyer. The first four pages of Dr. Meyer's review, which includes her clinical pharmacology synopsis and recommendations, are reproduced in this review as Appendix A.

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# Phase IV Study #3:
# Avelox® Clinical Experience Study (Protocol #100268)

## Regulatory Materials Reviewed

**NDA 21-334 volumes 1.1-1.8, submitted also to NDA 21-085/ NC, volumes 29.1-29.8**
**NDA 21-085 (Avelox), approval letter dated December 10, 1999**
**NDA 21-085 (Avelox), MO safety reviews**
Consultation from Division of Drug Risk Evaluation II, review of protocols for Avelox phase IV active surveillance programs (observational studies in Germany and US), dated March 21, 2000

## Objective

To further evaluate the safety and efficacy of Avelox 400 mg tablet, once daily, for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis or community acquired pneumonia (of mild to moderate severity).

> *MO COMMENT: The above statement of objectives is taken verbatim from the sponsor's study report. It should be noted that the description of this phase IV commitment stated in the approval letter and presented in the **Regulatory Background** above is a request for information regarding adverse event incidence. For this reason this review discusses safety issues only.*

A primary focus of the study was to detect any ventricular tachyarrhythmias or episodes of *torsades de pointes* that occurred.

## Design

This was a non-randomized, open-label, multicenter evaluation of adverse events among out-patients who received Avelox 400 mg daily for 5 days for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) or for 10 days for acute bacterial sinusitis or community acquired pneumonia (CAP). It was planned to enroll at least 15,000 out-patients at over 5000 sites in the continental US and Puerto Rico. Additional inclusion criteria were age $\geq$ 18 years and the provision of informed consent. Noteworthy exclusion criteria were concomitant medication with a class IA or class III anti-arrhythmic and congenital prolongation of the QT interval.

> *MO COMMENT: The lack of randomization in this study raises a question about how patients were considered suitable for enrollment. This issue was raised with the sponsor at the time the protocol for this study was reviewed by FDA. The study report does not describe a screening process. It cannot be determined if patients were enrolled as they presented to the individual centers or if a selection process took place that excluded certain patients other than those who failed to meet the entry criteria.*

Based upon a clinical diagnosis of one of the three infections listed above, a patient was prescribed either a 5 or 10 day course of Avelox 400 mg. Once written informed consent was obtained, the patient was enrolled in the study at Visit 1. Follow-up assessments were made at Visit 2, 48 hours after completion of study drug. This took place in the physician's office or by telephone.

Patients were monitored for adverse events by non-specific questioning at each visit. An assessment was to be made of the seriousness, intensity, and relationship to the administration of trial medication. In case of a severe adverse event, drug treatment may have been discontinued. Standardized definitions were provided for adverse event, serious adverse event, relationship to study drug (probable, possible, unlikely, none, not assessable), and intensity (mild, moderate, severe). Information was recorded on a Case Report Form.

A special safety committee called the Critical Events Committee (CEC) was formed to receive and review clinical events that occurred in the course of the study that could possibly represent an arrhythmia. This was composed of two independent experts in cardiology and drug safety. Those events considered to be of special interest to the CEC were considered 'critical' and are presented below:

1. *Torsades de pointes*
2. Ventricular arrhythmia
3. Sudden death
4. Cerebral vascular accidents
5. Syncope
6. Palpitations
7. The recording of an ECG
8. The hospitalization of a patient

Data regarding a critical event were collected on a standardized Critical Event Form. Each member of the CEC independently reviewed and adjudicated each critical event using a standardized Adjudication Algorithm. When an ECG was obtained on a patient, the actual ECG, or when not available the clinical report, was reviewed to determine whether there was evidence of a ventricular arrhythmia. After independent review, the members of the CEC discussed their opinions and reached consensus regarding each critical event. The results of the adjudication were then communicated to Bayer.

The MO reviewed both the Critical Event Form and the Adjudication Algorithm. The Critical Event Form collected information to determine if an arrhythmia or QT prolongation occurred, and if there were cardiac or other risk factors present that might explain the event. The Adjudication Algorithm determined if an event were critical, if there were an ECG tracing indicating an arrhythmia, and if there were other evidence of an arrhythmia. If there were any evidence of an arrhythmia, the relationship of any arrhythmia to the observed clinical event, and the presence of a number of other possible

causes for the arrhythmia was also assessed. The final step was to determine the nature of the causal relationship of Avelox to the observed arrhythmia as either 'possible, unlikely, none, or not assessable.' The results of the first three questions from all Adjudication Algorithms were tabulated and appended to the CEC Report.

*MO COMMENT: Review of the results of the first three questions of the Adjudication Algorithm shows that it is not possible to determine which patients had an ECG performed. The question on the Adjudication Algorithm is, 'Is there an ECG indicating an arrhythmia?' The possible responses are 'yes' or 'no.' Review of tabulated results for all critical events shows that this question is answered 'no' for every critical event reported. It cannot be determined if there were an ECG performed and it was without evidence of an arrhythmia or if there were no ECG performed. It should be noted that no ECG was required or recommended in this study, and obtaining one was done at the discretion of the individual investigator. For further discussion of this issue, the reader is referred to the section below entitled **RESULTS/Adverse events/Special safety issues.***

*Attributability was scored differently for events adjudicated by the CEC compared with other adverse events. The CRF completed by the investigators described 5 categories of attributability, 2 of which ('probable' and 'possible') were affirmative responses. The CEC Adjudication form described 4 categories of attributability, only 1 of which ('possible') was an affirmative response. There was no opportunity for the CEC to describe an event as 'probably' related to moxifloxacin administration.*

## Results

### Demographics

A total of 18,409 patients from 3377 centers were enrolled in a non-randomized design. According to the sponsor, 18,374 were treated with Avelox 400 mg once daily. Patients ranged in age from 6 to 97 years with a mean age of 48.5 years. In the population studied, 86% were Caucasian, 7% were Black, 1% were Oriental, and 5% were Other. About 60% of the patients were female and 40% were male. The safety database included 18,374 patients. Of this population, 1387 (7.5%) had CAP, 6039 (32.9%) had AECB, 10,822 (58.9%) had sinusitis, and 126 (0.7%) had an unknown diagnosis.

*MO COMMENT: That patients were not randomized for enrollment in this study introduces the possibility of selection bias. The MO attempted to better characterize the severity of presenting infection and the underlying health of the population studied by analyzing certain aspects of acute presentation and of medical history of the patients enrolled. Those results are presented below:*

ACUTE PRESENTATION

| | |
|---|---|
| CAP | Patients presenting with fever 49% |
| | Patients presenting with nasal congestion 80% |

| | |
|---|---|
| SINUSITIS | Patients presenting with fever 19%<br>Patient presenting with nasal congestion 95% |
| AECB | Patients presenting with cough 99%<br>Patients presenting with dyspnea 56%<br>Patients receiving chronic steroids at enrollment 7%<br>Patients requiring steroids for acute management 1% |

MEDICAL HISTORY
TOTAL STUDY POPULATION

| | |
|---|---|
| Most common pre-existing diagnoses (descending order) | Hypertension 23%<br>Diabetes mellitus 7%<br>Atherosclerotic heart disease 4.1%<br>Previous MI 1.7% |
| Most common chronic medications (descending order) | Beta-2 agonists 8.4%<br>Steroids 6.7%<br>HMG CoA reductase inhibitors 5.7% |

The data describing the underlying disease burden of the study population suggests that a small minority (6.7%) of chronic pulmonary patients had disease severe enough to require chronic steroids. Similarly, there was only a small proportion of patients with diabetes (7%). These findings suggest that this study population may not represent the full spectrum of those requiring antmicrobial therapy for respiratory tract infections.

**Disposition**

***Number of patients in safety database***

Generally the safety database should include all patients who received any study drug. As noted on Page 9 of the protocol draft dated 3/13/00 and submitted with this study report, this was the intent of the sponsor. The protocol states,

> *'The event frequency rates will be calculated as the proportion of patients who experience the event among the total number of patients who took at least one dose of the treatment.'*

The safety population (18,374) was smaller than the population enrolled (18,409) by 35 patients. As noted in Section 11.2 of the study report, the sponsor stated that 18,374 is the number of patients who were treated with moxifloxacin 400 mg daily. Review of tables presenting safety data (Tables of 14.3.1 series) showed that 18,374 was the total number of patients on whom safety was reported.

Review of Table 14.1/1 Disposition by diagnosis (Volume 1 of 8, page 2-42) showed that of the total study population of 18,409 patients, there were a total of 35 who did not complete the trial. It cannot be determined from the study report or from the tables

presenting safety data whether 35 patients were excluded from the safety database because they did not receive drug or if they did not complete the trial.

In Section 9.8, the study report describes 35 patients of the total enrollment for whom there was no Visit 2 form completed. Reasons for a lack of Visit 2 form presented by the sponsor are shown in Table 1 below:

Table 1: Patients with no Visit 2 form completed post treatment

| Reason | No. Patients |
|---|---|
| No information* | 15 |
| Physician refused to comply with request | 7 |
| Patient withdrew consent | 1 |
| Physician unable to contact patient | 3 |
| Physician could not identify patient | 8 |
| Physician dropped patient from study (no informed consent) | 1 |
| TOTAL | 35 |

*Principle investigator no longer at site or site unavailable for contact

These statements in the study report suggest that 35 patients were excluded from the total enrollment of 18,409 because there was inadequate follow-up on these patients for the reasons listed above. There are no statements in the study report that distinguish between two subpopulations of 35 patients, one excluded from the total population for lack of exposure to drug, another excluded from the total population because of lack of follow-up. Thus the possibility is raised that 35 patients were excluded from the safety database because they did receive some study drug and were then lost to follow-up. Reasons for loss-to-follow-up can include adverse events. If that is the case, the safety database then failed to capture 35 (0.2%) patients.

> *MO COMMENT: In a facsimile dated March 14, 2001, the MO requested that Bayer provide the patient numbers of those 35 patients excluded from the safety database and the patient numbers of those 35 patients for whom there was no Visit 2 Form (lost to follow-up). The sponsor's reply confirmed that there was one list of 35 patients excluded from the safety database. The patient identification numbers of those 35 individuals were submitted with the reply.*

***Patients accrued after data cutoff date***

Between April 10 and June 26, 2000, a total of 18,409 patients were enrolled. An additional 68 patients accrued after the cutoff date for the CEC review (June 26, 2000). The study report states that these patients' records were reviewed and found not to include any critical events.

> *MO COMMENT: On March 12, 2001, The MO requested that the sponsor clarify these contradictory statements. In a reply dated March 19, 2001, the sponsor*

*stated that these 68 patients were not included in the overall safety review for this study. Reports on two patients of the 68 were forwarded to the CEC for review and adjudication in a manner similar to any other patient reports sent to the CEC. The sponsor explained that the CEC functioned independently in this regard.*

***Patients with early V2***

At the end of patient enrollment, there were 1917 (10.4%) patients in whom the follow-up visit (Visit 2) was conducted prior to the end of study drug treatment (eg. a Visit 2 CRF was completed on day 6 of a 10-day treatment course). In each of these 1917 cases, the investigator was contacted by telephone and information similar to what was requested on the Visit 2 CRF was collected. There were 2 cases for whom such follow-up information could not be obtained.

*MO COMMENT: In 10% of the patients enrolled, follow-up safety information was collected retrospectively by telephone instead of prospectively on a standardized form. The study report does not comment on any differences in safety reporting in this subpopulation compared to the patients for whom Visit 2 took place within 48 hours after drug completion, as was specified in the protocol.*

***Exposure***

There were no active measures, such as pill counts, used in this study to monitor compliance. As noted above 7.5% patients enrolled had CAP, 32.9% had AECB, 58.9% had sinusitis, and 0.7% had an unknown diagnosis. The course of therapy for CAP and sinusitis was moxifloxacin 400 mg daily for 10 days, and for AECB was moxifloxacin 400 mg daily for 5 days. Interestingly, across these three groups of patients the proportion that received a course of therapy that was different from what was specified in the protocol was constant. These data are presented in Table 2 below:

Table 2: Proportion of patients receiving course of therapy other that specified in protocol

| INDICATION (N) | # DAYS | % PTS RECEIVING PRESCRIBED COURSE | % PTS RECEIVING OTHER THAN PRESCRIBED COURSE |
|---|---|---|---|
| CAP (N=1387) | 10 | 72 | 28 |
| AECB (N=6039) | 5 | 73 | 27 |
| Sinusitis (N=10,822) | 10 | 73 | 27 |

*MO COMMENT: If the results of this observational study can be generalized to include all moxifloxacin use, it appears that approximately 75% of patients receive the course of drug recommended. These data do not provide information regarding how many patients received more and how many received less drug than prescribed. The proportion of patients who received the prescribed course of therapy does not appear related to the duration of treatment (5 or 10 days).*

There were 38 patients enrolled who received more than 10 days of study drug. Thirty-four patients received 11-15 days of therapy, and 4 patients received >15 days of therapy with moxifloxacin.

**Adverse Events**

***General***

Adverse events were experienced by 3257 (17.7%) patients in this study. A total of 127 (0.7%) had serious adverse events and there were 6 (0.03%) deaths. There were 1089 (5.9%) patients who withdrew from the study due to an adverse event. These safety data from the study under review were compared with the rates of the same events from the safety database of NDA 21-085 (Avelox tablet, approved 12/10/99). This comparison is presented in Table 3 below:

Table 3: Comparison of safety: ACES #100286 and NDA 21-085

| | ACES (Protocol #100286) | NDA 21-085 |
|---|---|---|
| **Number of patients exposed to moxifloxacin** | 18,000 | 5,000 |
| All Aes | 17.7% | 46% (drug related: 32%) |
| Deaths | 0.03% | 0.45% |
| Sudden death | 0.01% | 0.02% |
| Withdrawals due to AE | 5.9% | 4% |
| Serious AE | 0.7% | 4% |

*MO COMMENT: Reporting rates were generally lower for the postmarketing study that is the subject of this review. Some of these observations might be explained by the differences in design between a phase IV observational study and the more structured, multivisit design of a phase III clinical trial. Inspection of these data, particularly the death rates, might also suggest differences in the underlying health or in the severity of the presenting infection between the two study populations. The reader is referred above to the **RESULTS** section, **Demographics** subsection for a discussion of these aspects of the population enrolled in the study under review.*

***Deaths***

There were six deaths during this study. The study report stated that none were thought to be study drug related, but rather, were ascribed to the patient's underlying disease. The study report also stated that of the six deaths, only two patients had an event that might represent a ventricular arrhythmia. One of these patients died after a single dose of moxifloxacin, which the study report concluded would be a very unlikely case of *torsades de pointes*. The other occurred in a patient with end-stage renal disease and heart failure and the patient died at home suddenly. In this case, the study report stated, *torsades de pointes* could not be excluded.

*MO COMMENT: The MO reviewed the narratives of all six patients who died. Five of these patients were over 65 years old and three were over 75 years old. For four of these deaths the MO concurred that there was no relationship to study drug. In two of these cases the MO did not think that the relationship to study drug was 'none,' and therefore cannot concur with the statement made in the study report.*

*Patient #5 of investigator #3359 was a 76 year old woman with chronic obstructive lung disease given moxifloxacin on June 12, 2000 for AECB. Later the same day, the patient was found collapsed at home by a family member, CPR was initiated, and emergency medical technicians found the patient asystolic when they arrived at the home. After forty minutes of advanced life support measures, the patient was brought to the emergency room where she was pronounced dead on arrival. The death certificate stated that the patient died of respiratory failure subsequent to chronic obstructive pulmonary disease. The narrative submitted by the sponsor stated that the adverse event, respiratory arrest, has an unlikely relationship to study medication. The MO review of this narrative determined that this was a case of sudden death. This patient had an unobserved arrest, and whether it was primarily cardiac or respiratory is unknown. The patient was experiencing a flare of her chronic obstructive lung disease, and it is therefore possible she experienced a worsening of her respiratory function that resulted in her death. It is noteworthy that at a physician visit the same day, however, she was considered well enough to be managed as an out-patient. The possibility that she experienced an anaphylactic reaction to her first dose of moxifloxacin might also explain a sudden respiratory decompensation (see below for additional discussion of anaphylaxis and other allergy-related adverse events). Since the patient only took a single dose of moxifloxacin, it is less likely that cardiac repolarization was affected to such an extent that the patient experienced torsades de pointes that resulted in sudden death. Whether she had another malignant cardiac arrhythmia due to hypoxia or electrolyte abnormalities is unknown. The MO determined that the relationship of this death to study drug administration is 'not known,' rather than 'none.'*

*Patient #2 of investigator #1183 was a 61 year old man with end-stage renal disease, COPD, CHF, and poorly controlled diabetes who had a documented left bundle branch block prior to starting treatment with moxifloxacin. The patient started treatment for AECB on April 14, 2000 and died on April 18, 2000. The date that he stopped taking moxifloxacin is not known. Though the narrative submitted does not state that the patient died suddenly, this is the only one of the six patients who died with end stage renal disease, and therefore is likely to be the one referred to in the study report. As noted above, the sponsor stated that torsades de pointes could not be ruled out as a cause of death in this patient. Since it is not known if the patient were still receiving moxifloxacin at the time of death, the relationship to study drug cannot be assessed.*

***Serious adverse events***

The study report stated that there were 127 (0.7%) patients for whom a serious adverse event was reported. None of these serious adverse events was considered by the sponsor to be study drug related.

*MO COMMENT: The MO reviewed the narratives of the 127 patients for whom serious adverse events were reported. The majority of these events (n=80 or 63%) were exacerbations of the underlying respiratory tract illness for which the patient was receiving moxifloxacin. The attributability of these events to study drug administration is a matter of efficacy review that will not be addressed here.*

*The remaining 47 reports of serious adverse events were reviewed to determine the type of event and the attributability to moxifloxacin. Of these 47, there were 11 patients with serious adverse events that were described in the narratives as possibly or probably related to moxifloxacin administration. The MO cannot concur with the study report statement that none of the serious adverse events was thought related to study drug.*

*Of these 11 patients, 5 reported dizziness. There was no mention of ECG data in the narrative for four of them. The fifth patient with serious adverse events- near syncope and dizziness- that were thought probably related to moxifloxacin did have ECG data. Her case is presented below.*

*Patient #3 of investigator #4380 was a 70 year old woman who received moxifloxacin from June 12 to June 18, 2000 for acute sinusitis. She had a past medical history remarkable for hypertension for which she took nifedipine and hydrochlorothiazide. On June 19, the patient experienced dizziness and near-syncope for which she was hospitalized. ECG on June 19 showed normal sinus rhythm, right bundle branch and left anterior hemiblock (bifasicular block) and QTc 409 msec. ECG on June 20 showed QTc 504 msec. Serum potassium levels on the 19th and 20th were both normal. The adverse events reported for this patient were near syncope (serious) and dizziness. This patient's case was adjudicated by the Critical Events Committee and these adverse events were both thought to have a 'probable' relationship to study medication. The MO concurred with this assessment of attributability, and noted that this case represented a serious adverse event probably related to study drug. There was no comment from the CEC regarding the likelihood that this patient's pre-existing bifasicular block was a factor in the development of dizziness and near syncope, though this may be considered a possible factor as well. Bradyarrhythmias, particularly complete or third degree AV block, are also considered a risk factor for torsades de pointes.*

*In addition, this patient was noted to have a QTc >500 msec that was not recorded as an adverse event of any kind. The MO considered this patient a case of prolongation of QT interval for which attributability is somewhat complex. The longest QT interval measured for this patient was documented perhaps 36-48 hours after she took her last dose of moxifloxacin. Recent*

*pharmacokinetic/pharmacodynamic studies have shown that the time of maximum QT prolongation was observed to occur 3-4 hours after Cmax in approximately 60% of patients studied. Little is known about the kinetics of myocardial drug concentration. These observations raise the possibility that maximum QT prolongation may occur well after the patient takes a last dose of moxifloxacin, though this matter remains speculative at this time.*

The study report stated categorically that there was 'no apparent difference in adverse events in relation to sex and age.'

*MO COMMENT: The MO sought to analyze the database for the rates of adverse events by age group (ie. <65 years, 65-74 years, >75 years). Though the sponsor presented data on numbers of subjects reporting any adverse event in each of these age groups, there was no information provided regarding the numbers of individuals enrolled in each of these groups. Thus it was not possible to calculate the rates of adverse events by age group.*

***Patients who received more than 10 days of study drug***

Among the thirty-eight patients who received more than 10 days of moxifloxacin, there were four (10.5%) who experienced adverse events, compared with 17.7% in the overall patient population. One patient had thrush, one experienced GI distress, one had abdominal pain, and one diarrhea and vomiting. All patients with adverse events did discontinue study drug because of the adverse event except for the patient with GI distress.

***Pediatric patients***

There were 47 patients under the age of 18 years who were enrolled into the study and treated with moxifloxacin. The mean age of these patients was 15 years, the youngest was six years old. There were six patients in this population who experienced an adverse event. Three reported nausea, one GI upset, one lightheadedness, and one diarrhea and constipation. The adverse event rate was 12.8% in this population compared to an adverse event rate of 17.7% in the study population overall. One patient with nausea discontinued study medication due to the adverse event. There were no serious adverse events or critical events in this population.

## Special Safety Issues

### Cardiac safety and the Report of the Critical Events Committee (CEC)

As noted in the study report, the sponsor undertook this trial primarily to detect ventricular arrhythmias and/or episodes of *torsades de pointes*. This was an observational study intended to reflect clinical practice. As such, it is expected that data collection might not be as intensive as it would be in a prospective, controlled phase III clinical trial. Nonetheless, it is important to recognize what data were and were not available from this population. Table 14.3.1/1D from the submission presents the numbers of patients from whom an ECG was recorded during the study. Those results are reproduced below in Table 4:

Table 4: Patients who had ECG recorded during the study by diagnosis

| DIAGNOSIS | PATIENTS ON WHOM ECG PERFORMED N (%) | | |
|---|---|---|---|
| | YES | NO | UNKNOWN |
| Unknown | 1 (0.8) | 115 (91.3) | 10 (7.9) |
| CAP | 27 (1.9) | 1328 (95.7) | 32 (2.3) |
| AECB | 71 (1.2) | 5789 (95.9) | 179 (3.0) |
| Sinusitis | 81 (0.7) | 10401 (96.1) | 340 (3.1) |
| **OVERALL** | 180 (1.0) | 17633 (96.0) | 561 (3.1) |

Inspection of Table 4 demonstrates that in this observational study designed to detect ventricular arrhythmias, 1 % of the 18,000 patients enrolled had an ECG performed. The sponsor also collected data on certain clinical events thought representative of possible arrhythmias. Such events were reviewed and adjudicated by the Critical Events Committee (CEC) as described in the section above entitled **DESIGN**. The report of the CEC is reviewed below.

There were 843 patients whose data were reviewed by the CEC. Of these, 546 had data that were determined by the CEC to not include a critical event. Of these patients with non-critical events, 411 had simple dizziness, lightheadedness, or similar events without any evidence of arrhythmia, hospitalization, or ECG obtained. A summary of the non-critical events is presented in Table 5.

Table 5: Non-critical events (n=546)*

| SYMPTOMS/DIAGNOSES | N |
|---|---|
| Dizziness, lightheadedness, woozy | 411 |
| Hospitalized for worsened infection (without ECG with arrhythmia) | 31 |
| Dyspnea, heart failure, worsened lung disease | 30 |
| Chest tightness or pain | 28 |
| Sent in error (eg. ECG prior to Avelox) | 13 |
| Confusion or disorientation (without neurological findings) | 7 |
| Anxiety or tremor | 3 |
| Swelling or hives | 2 |
| Throat pain | 2 |
| Single reports- epistaxis, hemoptysis, motor vehicle accident, neck surgery, colonoscopy, lung cancer, hernia surgery, migraine, rash, cellulitis, ovarian cyst, sinus surgery, dehydration, tingling, visual abnormality, pregnancy | 16 |

*By definition, none had a history of death, ECG, palpitations, syncope, or hospitalization-except for bronchitis/sinusitis/pneumonia worsening and no arrhythmia on ECG.

There were 297 reports considered to represent critical events. The mean age of these patients was 55 years; 205 were females and 92 were males.

*MO COMMENT: The mean age of the patients who experienced critical events was older than that of the total study population (55 v. 48.5 years). Similarly, the proportion of those who experienced a critical event who were female (69%) was somewhat higher than the proportion of females in the total study population (60%).*

As noted above, there were six deaths in the study population. The remaining 291 non-fatal critical events are summarized in Table 6.

Table 6: Non-fatal critical events (n=291)

| SYMPTOM/DIAGNOSIS | N |
|---|---|
| Palpitations/racing heart/tachycardia (25 with ECG, 112 without ECG) | 137 |
| Hospitalizations (39 with ECG, 41 without ECG) | 80 |
| Chest pain and ECG | 21 |
| Syncope or presyncope (8 with ECG, 9 without ECG) | 17 |
| Dizziness or lightheadedness plus ECG | 9 |
| Shortness of breath or equivalent plus ECG | 7 |
| Routine ECG or ECG for hypertension | 14 |
| ECG for suspected atrial fibrillation or sinus bradycardia | 4 |
| Abdominal pain plus ECG | 2 |

Of the 291 patients who had non-fatal events that were possibly representative of an arrhythmia, 129 (44%) had an ECG performed. The report does not state the proportion of these for which the original ECG tracing was available for review by the CEC, and for what proportion the CEC had to rely on clinical reports of ECG tracings. For events that are thought to be particularly suggestive of ventricular arrhythmia – palpitations and syncope- 21% had ECGs performed. Patients with critical events were more likely to have had an ECG performed than were the patients in the general study population. However, for more than half of these patients no arrhythmia testing was performed.

The CEC found that none of the ECGs recorded and reviewed demonstrated evidence of a ventricular tachycardia. The report stated that only one ECG showed a new QTc prolongation of >500 msec. This was seen in patient #4 of investigator #1804 who was found to have a QTc of 510 msec. This patient was admitted to the hospital for wheezing and had normal sinus rhythm with PVCs that had been present prior to moxifloxacin administration.

*MO COMMENT: The MO reviewed the line listing 16.2.7/1A which showed whether or not a case was adjudicated by the CEC and the result of the*

*adjudication. For patient #4 of investigator #1804, the listing shows that the events of wheezing and bronchospasm were considered not to have any relationship to study drug; there was no mention of QT prolongation among the list of adverse events for this patient.*

*MO COMMENT: Patient #3 of investigator #4380 (see above, Serious adverse events) is a second case of a patient identified in this study with a critical event and a QTc > 500 msec. These patients with prolonged QT intervals were not identified systematically by the MO. The data presented in the electronic submission was not amenable to such analysis. The total number of patients with QT intervals greater than 500 msec is not known. The MO has identified two.*

The conclusions of the CEC were the following:

1. There was no evidence of ventricular arrhythmia in the ECG tracings or the reports reviewed by the CEC.
2. None of the hospitalizations was associated with identified ventricular arrhythmias.
3. There were two cases treated with moxifloxacin in which a ventricular tachycardia may have been present. Since one occurred after a single dose of moxifloxacin, this is very unlikely to have been a case of *torsades de pointes*. The other of these two cases had end-stage renal disease and heart failure and died at home suddenly, therefore *torsades de pointes* cannot be excluded.

*MO COMMENT: MO conclusions following review of the CEC Report are the following:*

1. *Less than half (44%) of the 291 patients adjudicated by the CEC had ECG tracings performed on them. For those with palpitations, syncope or near syncope, 21% had an ECG.*
2. *Of the 80 patients hospitalized, only half (49%) had ECG tracings performed on them.*
3. *Of the six patients who died, there were two sudden deaths. It is unlikely that the patient who died after receiving one dose of moxifloxacin experienced a ventricular arrhythmia attributable to moxifloxacin. The possibility does exist that this patient experienced A hypersensitivity reaction to the drug. There is not adequate information to assess attributability in the second patient who died suddenly.*
4. *There were two patients who experienced QTc prolongation >500 msec. These events did not get reported among the adverse events listed for either patient. Given that the recording of an ECG was considered a critical event, it is not clear why these episodes of QTc prolongation were not reported. Because it was not possible for the MO to identify these episodes of QT prolongation by systematic analysis, it cannot be concluded that all have been identified.*

*As noted above, draft labeling submitted with NDA 21-334 includes a new statement for the Avelox tablet label that is based on the results of study 3. That statement is reproduced below:*

> In a US postmarketing observational study, monitoring the safety experience of AVELOX Tablets in more than 18,000 outpatients, no evidence of increased cardiovascular mortality or morbidity was observed with moxifloxacin treatment.

*Following review of the data submitted from study #100268, it is not possible to concur with or refute this statement. It should not be included in the label. This position was conveyed to the company during labeling discussions and alternative wording was agreed upon for inclusion in the WARNINGS section of the label.*

**Anaphylaxis**

Spontaneous safety reporting for moxifloxacin in the early postmarketing period suggested that there were a substantial number of reports of hypersensitivity reactions characterized by facial or laryngeal edema and/or hypotension, ie. anaphylaxis. Attempts to systematically review this issue included research in the medical literature, periodic consultation with OPDRA staff regarding spontaneous reporting rates for anaphylaxis and related events, and an analysis of data from the active surveillance study under review for rates of anaphylaxis and related events. Information from each of these sources is discussed below.

Among the drugs that most commonly cause anaphylaxis are penicillin (PCN) and radiocontrast media (RCM). Anaphylactic reactions occur in 4-15 of every 100,000 penicillin treatment courses or 40-150 per million courses (Weiss and Adkinson in Mandell et al Principles and Practice of Infectious Diseases 2000, p. 299). Less than 10% of such reactions are fatal. However PCN and RCM together account for the vast majority of US deaths from anaphylaxis each year (Bochner and Lichtenstein, 1991. Anaphylaxis, New Eng J Med 324: 1785-90). Data from the 1980s showed that of the 1500 anaphylaxis deaths that occur annually in the US, approximately 400 are due to penicillin and 900 due to radiocontrast media. The other causes of anaphylaxis deaths include foods, latex, and insect stings (Neugut, Ghatak, and Miller, 2001. Anaphylaxis in the United States, Arch Int Med 161: 15-21).

> *MO COMMENT: It is not clear that penicillin and radiocontrast media will still continue to account for the vast majority of anaphylaxis deaths as penicillins are used less commonly, and since low osmolarity contrast materials have been introduced into the practice of diagnostic radiology.*

The most recent postmarketing safety review of serious anaphylaxis rates reported for moxifloxacin was requested from OPDRA Division of Drug Risk Evaluation II in February 2001. The FDA spontaneous reporting system, Adverse Events Reporting

System (AERS), was searched twice for this review (February 15 and March 1, 2001), and utilization data were obtained from the IMS Health National Prescription Audit database. Reporting rates of serious anaphylaxis per [redacted] US oral prescriptions were calculated for moxifloxacin and other fluoroquinolones. Table 7 presents the rates for moxifloxacin and gatifloxacin, both approved in December 1999 for a number of respiratory tract indications, and compares these with the published rates for penicillin.

Table 7: Comparative rates of serious anaphylaxis relative to drug exposure

| Drug | Serious Anaphylaxis per Million Exposures US | Raw 14-Month Counts of US Cases Serious Anaphylaxis | Projected PO Rx Dispensed by US Retail Pharmacies During First Year |
|---|---|---|---|
| Moxifloxacin* | 22.4 | 19 | [redacted] |
| Gatifloxacin* | 7.2 | 13 | |
| Penicillin† | 40-150 | NA | |

*Source: OPDRA consult March 2001; based on spontaneous reporting, oral administration only

† Source: published literature (Weiss and Adkinson 2000 op cit), This is based in part on an active surveillance study of anaphylaxis rates observed in patients receiving monthly intramuscular benzathine penicillin for rheumatic fever prophylaxis. In this population, serious anaphylaxis events were observed to occur in 120 patients per million exposed (International Rheumatic Fever Study Group, Lancet 199; 337:1308-1310).

There are some limitations to the comparisons that can be made between the data presented above for fluoroquinolones and penicillin. Table 7 presents data for two new fluoroquinolones based on the FDA spontaneous reporting system. The sources of the data presented for penicillin appear in part to be derived from active surveillance. It should also be noted that the data presented for fluoroquinolones reflect the first year if use of these agents, while the data for penicillins are derived from decades of use. It is reasonable to assume that active surveillance results in higher reporting rates than does spontaneous reporting. The data from the study under review, a prospective, active surveillance study, provide some insight into this issue.

In the listings of adverse events for Study #100268, there were line listings of events that may be considered representative of anaphylaxis. The rates of these adverse events are provided in Table 8. There was no information regarding previous exposure to quinolones in these patients.

It should be noted that it is uncertain whether the terminology dictionary used for coding adverse events in this study included the term "anaphylaxis." This may explain the use of the term "anaphylactoid reaction," a syndrome clinically indistinguishable from anaphylaxis but mediated by a different immune mechanism

Table 8: Rates of adverse events suggestive of anaphylaxis

| EVENT | No. of patients (%) |
|---|---|
| Vasodilatation | 29 (0.16%) |
| Urticaria | 28 (0.15%) |
| Face edema | 19 (0.10%) |
| Allergic reaction | 7 (0.04%) |
| Tongue edema | 4 (0.02%) |
| Anaphylactoid reaction | 1 (0.01%) |
| Larynx edema | 1 (0.01%) |

Because one patient experiencing an anaphylactic reaction could result in a report of more than one of the above adverse events, it is not possible to determine the number of anaphylactic reactions that occurred in this study of 18,000 patients who received moxifloxacin. Some of the events above, such as vasodilatation, do not represent serious anaphylactic events in all patients who report it. One way to estimate the rate of serious anaphylaxis is to look at an event that defines this syndrome, such as laryngeal edema. It should be noted that limiting the scope to this adverse event may underestimate the number of cases of serious anaphylaxis. In this study, this event was reported in 0.01% of patients, a rate of 100 per million exposures. Data from this active surveillance study of moxifloxacin suggest that serious anaphylaxis occurs at a rate five times higher than the 22 per million noted from the FDA spontaneous reporting system. The data published for penicillin represent active surveillance rates, and rates of serious anaphylactic reactions for moxifloxacin may approach those published for penicillin. Because these findings are based on a relatively small number of cases, it is appropriate at this point to recognize the occurrence of anaphylaxis following administration of moxifloxacin with appropriate wording in the label, and continue to monitor the rate of such events.

The approved label for moxifloxacin currently includes a statement describing hypersensitivity reactions as a class effect. That wording is reproduced below:

> *Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Moxifloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management, including intubation, may be administered as indicated.*

New wording proposed by the MO to address the risk of anaphylaxis specifically due to moxifloxacin and to substitute for the above paragraph is presented below (Arial):

> Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving moxifloxacin therapy. Moxifloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Subsequent labeling discussions with the sponsor resulted in modification of this statement, and it is presented in its final form in the attached approved label.

## Medical Officer's Conclusions and Recommendations

### Cardiac events

This US-based active surveillance study was undertaken to provide additional safety information about moxifloxacin use in the out-patient setting. Collection of data regarding ventricular arrhythmias and, specifically, *torsades de pointes*, was the primary focus of the study. No malignant arrhythmias were identified among this population of more than 18,000 patients who received moxifloxacin, a drug known to prolong the QT interval. A noteworthy aspect of the study design is the lack of randomization and the resulting potential for selection bias in favor of healthy enrollees who may not adequately reflect the breadth of patients presenting for out-patient management of respiratory infections.

The results of the study do not suggest a high rate of malignant ventricular arrhythmias. The lack of such events in a population of 18,000 suggests that ventricular arrhythmias are unlikely to be more common than 1/6000 patients who receive moxifloxacin. This finding corroborates what was seen in the original NDA database of approximately 5000 patients. Additional characterization of the cardiac safety of moxifloxacin is limited in this study in which the majority of patients experiencing critical events did not have an ECG performed. The incidental identification of two patients with significant prolongation of the QT interval (>500 msec), raises the unanswered question of the total number of such 'outliers' in the safety database. The possibility that safety reporting excluded 35 patients that were lost to follow-up also limits what can be concluded from this surveillance study.

The sponsor has proposed additional wording in the Avelox label based on the results of this study. That wording is presented below:

> In a US postmarketing observational study, monitoring the safety experience of AVELOX Tablets in more than 18,000 outpatients, no evidence of increased cardiovascular mortality or morbidity was observed with moxifloxacin treatment.

Following review of the data submitted from study #100268, it is not possible to concur with or refute this statement. It should not be included in the label. This position was conveyed to the company during labeling discussions and alternative wording was agreed upon for inclusion in the WARNINGS section of the label.

### Serious hypersensitivity/anaphylaxis reactions

Analysis of spontaneous reporting in the first year of Avelox marketing showed that serious anaphylaxis reactions occurred at a rate of about 22 per million exposures. The active surveillance study reviewed here demonstrated a rate of anaphylaxis of about 100 per million exposures when laryngeal edema is used as a marker for this event. Use of

this marker may underestimate the rate at which these reactions occur following administration of moxifloxacin. These early data suggest that the rate at which patients experience anaphylaxis following administration of moxifloxacin may approach what has been reported for penicillin which is 40-150 per million exposures. Until additional data can be collected and analyzed, it would be prudent to inform prescribing physicians of this aspect of moxifloxacin safety. This can be accomplished by modifying a statement already in the approved label.

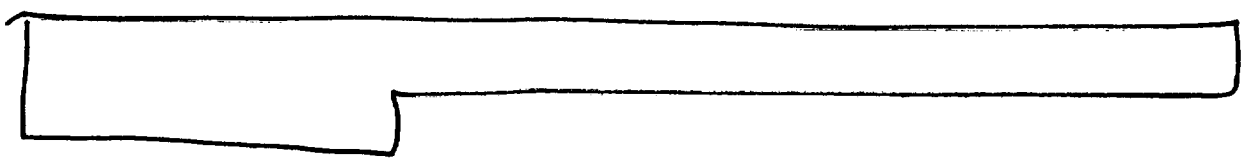
The approved label for moxifloxacin currently includes the following statement:

> *Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Moxifloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management, including intubation, may be administered as indicated.*

New wording proposed by the MO to address the risk of anaphylaxis specifically due to moxifloxacin and to substitute for the above paragraph is presented below (Arial):

> Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving moxifloxacin therapy. Moxifloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

This statement should be placed in the label following the discussion of the QT interval prolongation caused by moxifloxacin.



**APPEARS THIS WAY**
**ON ORIGINAL**

# Post-marketing Observational Study (September 1999 – May 2000) [PMOS]

## Introduction

The Post-Marketing Observational Study (PMOS) was an observational study that prospectively captured adverse events based on 16,000 subjects who received moxifloxacin for about 7 days in the outpatient setting in Germany and covers the period September 6, 1999 to May 26, 2000. The original objective of the study was to capture the response and relapse rates of patients with respiratory tract infections treated with moxifloxacin. The study was not originally planned to prospectively monitor patients for cardiac safety, although information on the safety and tolerability of the drug was also solicited. In December 10, 1999, when moxifloxacin was approved in the United States, this study was well underway in Germany.

The patients in this study are included in the larger PSUR database that incorporates safety from two observational studies with a summary of comprehensive worldwide spontaneous adverse event reports. However, the analysis of rates in the German study were calculated per patient whereas adverse event rate in the PSUR Report were based on sales of dose packages, assuming that each package represented one patient. This section summarizes the cardiac and allergic safety events from the German study database, as presented in the applicant's study report. Individual patient information was not submitted; there were no narratives of adverse events available for clinical review. The results of two independent expert reviews of the same safety database are also briefly summarized.

## Results

### Characteristics of Study and Study Population

Briefly, the data in this study differed from the data in the SPUR in that it was prospectively collected and included evaluation from the treating physician. However, reporting of adverse events was voluntary in content and scope and electrocardiographic (EKG) information was not sought. Compared to Protocol #100268 (the US-based observational study) the mean age of patients was slightly older (50 years), a greater proportion (58%) had a concomitant debilitating illness, a minority (16%) had an underlying respiratory condition (COPD and asthma), and more patients (9.7%) were diabetic. Fifty-seven patients (1.6%) received moxifloxacin as part of a combination regimen. Data on baseline symptoms, and steroid use were not provided.

**Drug exposure of patients in Study 2**

The duration of initial therapy is represented in the table below:

Table 9: Duration of therapy

| Treatment duration (days) | % |
|---|---|
| < 5 | 1.7 |
| 5 | 51.4 |
| 6-7 | 17.5 |
| 8-9 | 13 |
| 10 | 10.9 |
| <10 | 6.1 |

Ninety-nine percent of patients received the 400-mg dose. A second course of moxifloxacin was received by 218 (1.36%) of the 16000 patients.

*MO COMMENT: Most patients in this database received 5 days of the 400-mg dose. Information on adverse event rates associated with longer courses and higher doses of moxifloxacin in this database is limited.*

***Adverse Events (per patient rates):***

One thousand three hundred and two adverse events were reported in 918 of the 160007 patients (5.73%).

Comparison of this database to NDA and the two other Phase IV patient based reports:

Table 10: Comparison of safety: PMOS, ACES #100286 and NDA 21-085

| | PMOS | ACES (Protocol #100286) | NDA 21-085 |
|---|---|---|---|
| **Number of patients exposed to moxifloxacin** | 16, 000 | 18,000 | 5,000 |
| All Aes | 5.73 % | 17.7% | 46% (drug related: 32%) |
| Deaths | 0.08 % | 0.03% | 0.45% |
| Sudden death | -- | 0.01% | 0.02% |
| Withdrawals due to AE | 1.05% | 5.9% | 4% |
| Serious AE | 0.94 % (150 events) | 0.7% | 4% |
| "Cardiac" | 0.5% (77 events*) | -- | -- |

* 5 of these patients died. 2 patients with known cardiovascular disease died due to heart failure while on treatment, whereas 3 others died at 3, 4, 6 weeks post treatment. Three patients had syncope (0.02%).

*MO COMMENT: This adverse event rate was 3-fold lower than the adverse event rate in the US-based observational study. The adverse event rates in the two*

*observational studies were significantly less than the 46% rate in the clinical trials supporting the NDA approval, possibly indicating the magnitude of diminished sensitivity for adverse event detection in observational studies.*

**Withdrawals due to adverse events include the following:**

Table 11: Adverse Events

| Adverse event leading to withdrawal | # | (Serious) |
|---|---|---|
| Tachycardia | 6 | (0) |
| Shock | 3 | (0) |
| Palpitations | 3 | (1) |
| Heart failure | 1 | (1) |
| Atrial fibrillation | 1 | (1) |
| Syncope | 1 | (1) |
| Angina | 1 | (1) |
| CV disorder, unspecified | 5 | (1) |
| Chest pain | 1 | (1) |
| Heart failure | 1 | (1) |
| VPCs | 1 | (1) |
| Arrythmia | 3 | (0) |
| QT prolongation | 1 | (1) |

*MO COMMENT: None of the three cardiac events reported as arrythmias were considered serious. An additional three cases of "shock", presumably indicating hemodynamic instability, were likewise not considered serious. The identity of the patients could not be identified from adverse event listing provided.*

Drug related withdrawal rates were lower for this database (2.1%) compared to Study 3 (5.9%), even when missing information was considered withdrawn due to DRAE (3.7%).

*MO COMMENT: Since patient diaries were the basis for compliance assessment, this information may have been biased by patient reporting.*

**Cardiac events** (event based rates):
A summary of the cardiac events possibly related to QT prolongation include the following:
Table 12: Cardiac Events

| Event | N | Relationship to Moxifloxacin | | | | Severity of AE | | |
|---|---|---|---|---|---|---|---|---|
| | | Probable | Possible | Not related | No Information | Serious | Not Serious | No information |
| Angina | 2 | 1 | 0 | 0 | 1 | 0 | 1 | 1 |
| Arrythmia | 5 | 2 | 2 | 0 | 1 | 1 | 3 | 1 |
| Atrial fibrillation | 5 | 0 | 0 | 1 | 4 | 2 | 0 | 3 |
| Cardiac disorder | 9 | 4 | 2 | 2 | 1 | 2 | 6 | 1 |
| Chest pain | 19 | 1 | 2 | 13 | 3 | 4 | 13 | 2 |
| Abnormal EKG* | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Heart Failure | 13 | 0 | 0 | 13 | 0 | 10 | 2 | 1 |
| Hypotension | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| MI | 2 | 0 | 0 | 2 | 0 | 0 | 1 | 1 |
| Palpitation | 6 | 2 | 2 | 0 | 2 | 1 | 4 | 1 |
| Shock | 4 | 2 | 2 | 0 | 0 | 0 | 3 | 1 |
| SVT | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Tachycardia | 19 | 6 | 4 | 6 | 3 | 0 | 13 | 6 |
| VPCs | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| **TOTAL** | **88** | **19** | **16** | **38** | **15** | **22** | **48** | **18** |

*Of these 88 events reported in 77 patients, one event (see below) was related to QT prolongation and is described below.

*MO COMMENT: The proportion of patients with a cardiac adverse event who had an electrocardiographic study performed at the time of the adverse event could not be determined from the report. In 17% (15/88) of the cardiac events, the investigator's comment on relationship of the event to moxifloxacin was missing from the case report forms. Furthermore, the severity of 20% (18/88) of the cardiac events could not be determined.*

The only patient (Patient 15543) with a documented QT prolongation was a 35 year old male with pneumonia who experienced a "tachyarrythmia and QT prolongation". He had a history of aortic isthmus stenosis with post-stenotic anuerysm, s/p surgery, post-splenectomy, cardiac insufficiency, obesity and hypertension. He was receiving the following cardiac medications on baseline: captopril, furosemide and verapamil. He developed dyspnea and on follow-up for increasing dyspnea, was found to have an atrial fibrillation with QT prolongation, for which antibiotic treatment was changed to [redacted]. The QT interval remained prolonged when EKG repeated at 5 weeks. The sequence of documented electrocardiographic findings are shown below:

Table 13: Patient 15543

| Date | EKG | QT(msec) | QTc(msec) |
|---|---|---|---|
| 2 y pre tx | | 420 | 478 |
| Day 2 | "regular " EKG | | |
| Day 5 | AF w/ VR 140 | 320 | 485(D/Cdrug) |
| Day 6 | Sinus rhythm | | 482 |
| Week 5 | | 520 | |

*MO COMMENT: Although there was a paucity of electrocardiographic information for the rest of the database, the one case with a QT prolongation was amply documented, although a causal relationship cannot be concluded because the patient did have pre-existing QT prolongation associated with his anatomic cardiac lesions.*

**Deaths**

There were 13 deaths (0.08%); none were attributed to moxifloxacin by the investigators. The mean age of patients who died was 77.6 years. The cause of death was cardiac decompensation in 4, cancer in 2, CVA in 1 (84 and 89 y). There were three cases of "sudden deaths" for whom a recent electrocardiogram while on moxifloxacin was not available.

The cause of death could not be discerned from the COSTART term in the following cases:

Table 14: Deaths

| Patient | Age/sex | COSTART term | Underlying disease |
|---|---|---|---|
| 5939 | 69 / male | tremor, condition aggravated | chronic cor pulmonale |
| 13197 | 82 / male | dyspnea | |
| 13667 | 91 / female | tachycardia | |
| 15410 | 74 / female | condition aggravated | |
| 18408 | 60 / male | fever, dyspnea, choking | emphysema |

*no EKG ( unable to identify the 2 other deaths in whom an EKG was not done)

*MO COMMENT: As expected, patients who died were much older (mean age 77 years) than the mean age of the entire study group (51 years). The cause of death could not be determined in the three youngest patients. It was not possible to discern which patient did not have an electrocardiographic evaluation based on the information provided.*

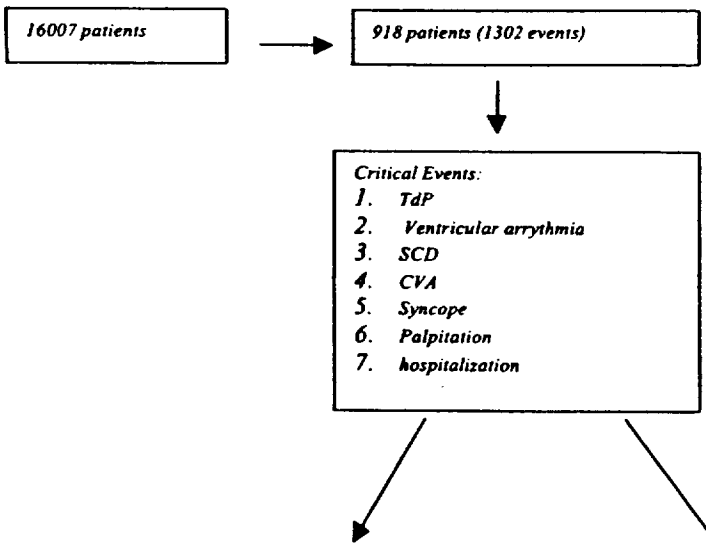
**Allergic Reactions**

Table 15: Allergic reactions

| Body as a Whole | N | % | (Drug -related*) | Serious | (SeriousDR) |
|---|---|---|---|---|---|
| Allergic reaction | 11 | 0.07 | 8 | 1/11 | 1 |
| Anaphylactoid | 1 | 0.01 | 1 | 1/1 | 1 |
| Fever | 11 | 0.07 | 1 | 7/11 | |
| Facial edema | 2 | 0.01 | 2 | | |
| Tongue edema | 1 | 0.01 | 1 | | |
| Pruritus | 12 | 0.07 | 9 | | |
| Rash | 15 | 0.09 | 14 | | |
| Urticaria | 4 | 0.02 | 3 | 1/4 | 1 |
| Vesicobullous rash | 2 | 0.01 | 2 | | |
| Asthma | 6 | 0.04 | 1 | 1/6 | |
| Dyspnea | 37 | 0.23 | 6 | 20/37 | 1 |

*MO COMMENT: Only one of the eleven allergic reactions was considered serious and drug related. Facial and tongue edema and "vesicobullous rash" were not considered serious adverse events, although they could represent anaphylaxis or Stevens Johnsons reactions. There is however, no report of laryngeal edema. There is no clinical data provided on which to base a clinical re-evaluation by the Medical Officer. The characterization of the event is dependent on the terminology chosen by the investigator and the reports therefore suffer from the same limitations that obtain in spontaneously reported adverse events. In terms of quality of information therefore, the prospectively collected information in this observational study is similarly voluntary, non-uniform and lacking in documentation of significant events.*

Summary of Expert Assessments:
Two independent expert reviews of the safety information were conducted. One review was undertaken by a Swedish expert. The other expert review was conducted by a Critical Events Committee (CEC) consisting of a cardiologist and a pulmonologist who independently assessed the data. These experts adjudicated the adverse event to assess a relationship of the adverse event to the QT prolonging potential of moxifloxacin and were the same individuals who assessed the US observational study. The CEC particularly looked for critical events that may indicate an underlying arrythmia: torsade de pointes (TdP), ventricular arrythmia (VA), sudden cardiac death (SCD), cerebrovascular event (CVA), syncope, palpitation, any hospitalization. Twenty-eight non -serious and 27 serious case reports of these critical events were reviewed in detail (please see Dr. Meyerhoff's review for details of CEC assessment mechanism). Both expert reviews could not find any evidence of unexplained ventricular arrythmias from the database, although the CEC could not exclude a relationship for 3 cases of sudden death due to lack of electrocardiographic documentation. The flowchart on the following page diagrams the patients' disposition.




| Serious Critical | N | (w/ EKG) |
|---|---|---|
| Deaths | | |
| Insufficient information | 3 | 0 |
| Lung cancer | 1 | |
| PE | 1 | 1 |
| CHF, dig tox | 1 | 1 |
| Death in hospital, AF | 1 | |
| Total | 7 | 3 |
| Hospitalization | | |
| Chest pain | 5 | 5 |
| CHF | 4 | 4 |
| Palpitations | 1 | 1 |
| Diabetes | 1 | 1 |
| Total | 11 | 11 |
| Syncope | 2 | ? |
| Palpitations | 7 | 3* |
| TOTAL | 27 | ~17 |

*QT prolonged

| Non-serious | N | (w/ EKG) |
|---|---|---|
| Syncope | 6 | 0 |
| Palpitation | 16 | 3 |
| Others | 6 | |
| TOTAL | 28 | 3 |

*MO COMMENT: The limitations of the observational study design and the information obtained from the study is highlighted by the expert reviews:*

1. *A substantial proportion of (36.4% or 20 of the 55) the critical events could not be assessed for QT prolongation.*
2. *The critical events committee reviewed only 36 the 150 patients with serious adverse events in the entire database.*

Conclusions:
The ability to exclude a relationship between the adverse events in this observational study and the QT prolonging potential of moxifloxacin is limited by the quality of the information gathered, since the study was not designed to obtain this information at the outset. The PMOS was designed to study efficacy and time to clinical response in respiratory infections, with voluntary adverse event reporting. To improve on adverse event reporting, effort was applied to follow-up on missing information by phonecalls to the treating physicians. While due diligence was applied in this following up on missing information, the study was well under way (on the 3rd month of an eight month study) when the commitment to phase IV studies evaluating cardiac safety of moxifloxacin was made. It is unlikely that any effort to improve information retrieval could have made any significant impact after the study was initiated.

Except for patients with cardiac events identified by the sponsor, there was no clinical information provided to allow a re-evaluation by the Medical Officer. Further, for the patients with cardiac adverse events, the line listings provide no detail that would exclude a causal relationship to the drug.

QT prolongation was identified in a patient with pre-existing QT prolongation. It can be argued that the pre-existing cardiac condition may have increased the likelihood that an electrocardiogram was requested after exposure to moxifloxacin, raising the purely arbitrary nature of electrocardiographic documentation within the context of an observational study.

The expert review identified three sudden deaths for which no EKG documentation is available. These patients could not be identified from the line listings provided.

With these reservations, this study did not identify any of fatal arrythmias in 16,007 patients, when this information was obtained in a manner similar to the spontaneous reporting system in terms of characterizing cardiac events.

There is insufficient information provided for the adverse events suggesting an anaphylactic reaction (shock, facial edema, tongue edema etc) on which to base a clinical diagnosis of this reaction.

## Medical Officer's Conclusions and Recommendations

If any statement on the potential for QT prolongation attributable to moxifloxacin is included in the label, the quality of information on which the conclusion of cardiac safety was based should be adequately characterized.

The risk of a fatal cardiac event attributable to moxifloxacin does not appear to preclude the approval of the uncomplicated skin and soft tissue infection.

With respect to anaphylaxis reactions, additional information beyond this observational study needs to be gathered before the label is modified beyond the current quinolone class-labeling statements.



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## Post-marketing Safety Update Report (June 1999 – June 2000) [PSUR]

**Exposure data included in this report:**

The safety database incorporates participants in two observational post-marketing studies (one conducted in Germany and one conducted in the USA), as well as all worldwide spontaneous adverse event reports for the period 22 June 1999 to 21 June 2000.

The two post-marketing observational studies included 24,600 patients during the period of this report.

Additional utilization was calculated based on worldwide sales of [redacted] dose packages (each containing either 5,7 or 10 tablets). The applicant assumed that each package represented one patient. The average number of doses per patient, calculated on the basis of package sizes marketed ranged between 7.1 and 7.8 for the first and second 6-month periods of this report.

IMS sales data were provided for comparison. During the reporting period, [redacted] prescriptions were recorded. Based on sales in the US, Bayer estimates that [redacted] exposures to Moxifloxacin were in US patients.

> *MO COMMENT: Overestimating the utilization based on these data may have occurred as a result of packages being lost, medication not taken, and the use of more than one package per patient.* [redacted]

### Organization of this Submission

Line listings were presented for all spontaneous reports, published and unpublished, reports from ongoing clinical trials and observational studies as received by "Global Drug Safety, Bayer AG."

From the spontaneous adverse event reporting database, all serious cases were included. Of the non-serious cases only those with 'unlisted' adverse events (AE) were included.

From the reports of ongoing trials and observational studies, only those serious cases rated by the investigator or the company as probably or possibly drug related were included.

> *MO Comment: Cases regarded as drug-related are likely more relevant in this submission than all cases particularly since no control population is available to assist in evaluating drug attributability.*

The information was presented in two sequential "periodic safety update reports" respectively covering the periods June 99 to December 99 and December 99 to June 2000. Data beyond June 2000 were not included.

The source of the AE reports includes 2 post-marketing observational studies in Germany and the USA, all clinical phase I to IV studies in progress during the reporting period, literature reports of adverse events, and spontaneous post-marketing adverse event reports worldwide.

## Overview of the Number and Rate of Adverse Event Reports

In the line listings of adverse event reports, each patient was represented once under the most serious condition. The applicant reports that rarely, patients had more than one adverse event determined to be most serious (maximum of two). These patients were listed twice in the line listings. The medical reviewer tabulated the cumulative number of adverse events. Since duplications were not indicated in the submission, cumulative numbers may slightly overestimate the numbers of patients with adverse events.

Table 16: Cumulative totals for all adverse events by reporting period

| | Serious | Non serious |
|---|---|---|
| Reporting period Jun 99- Dec 99 | 58 | 39 |
| Reporting period Dec 99-Jun 00 | 390 | 413 |
| **Total** | 448 | 442 |

Since the method of data acquisition differed depending on whether adverse events were spontaneously reported or whether adverse event data were solicited during observational or clinical studies, the reviewer calculated reporting rates for each data source to reflect these differences as shown below.

Table 17: Reporting period rates by data source (Jun 99-Dec 99)

| | Spontaneous reporting | | Literature | Post-marketing observational studies | Clinical phase I to IV studies |
|---|---|---|---|---|---|
| | Serious | Non serious | Serious | Serious | Serious |
| Events | 40 | 39 | 0 | 8 | 10 |
| Individual tablets (400mg) | 2,855,997 | 2,855,997 | 2,855,997 | | |
| No. of patients | 402,253 | 402,253 | 402,253 | 2,648 | 1,122 |
| Rate per $10^6$ patients | 99.4 | 96.9 | 0 | 3021 | 8913 |

*calculated based on average utilization of 7.1 tablets (400mg) per patient during this reporting period

Table 18: Reporting period rates by data source (Dec 99- Jun 00)

| | Spontaneous reporting | | Literature | Post-marketing observational studies | Clinical phase I to IV studies |
|---|---|---|---|---|---|
| | **Serious** | **Non serious** | **Serious** | **Serious** | **Serious** |
| Events | 263 | 413 | | 78 | 48 |
| Individual tablets (400mg) | 9,628,889 | 9,628,889 | 9,628,889 | | |
| No. of patients | 1,234,473* | 1,234,473* | 1,234,473* | 24,592 | **1468 |
| Rate per $10^6$ patients | 213 | 334 | 0 | 3172 | 32698 |

* calculated based on average utilization of 7.8 individual tablets (400mg) per patient during this reporting period

** The applicant reported 14964 patients enrolled in ongoing clinical phase I to IV studies of which 13496 were participants in the US post marketing observational study. The reviewer concluded that 1468 unique patients were involved in active clinical trials excluding the post-marketing observational studies.

*MO COMMENT:*
*Reporting rates for post-marketing observational studies were consistent for the two sequential 6 month periods. However spontaneous reporting rates doubled for severe adverse events from the first to the second six months of marketing. Notably reporting rates for serious adverse events (SAE) were between 15 and 30 times higher for observational studies than for spontaneous post-marketing reports. Thus a substantial rate of underreporting for SAEs is evident in the spontaneous AE reporting system.*

## Definition of Terms

1) Drug attributability- Drug attributability was determined by "Global Drug Safety, Bayer AG" based on WHO definitions as adapted by national centers participating in the WHO International drug monitoring program (September 1991). Drug associated events were those where there was a "reasonable possibility the experience may have been caused by the drug".

2) Serious adverse drug reaction (ADR)-These included death, life threatening experiences, hospitalization or prolongation of an existing hospitalization, a persistent or significant disability, a congenital anomaly and other events judged to jeopardize the patient and/or require medical or surgical intervention to prevent more serious harm.

## Synopsis of Findings in "Observational Studies"

The two observational studies included in this report have been reviewed individually. (See reviews by Drs. Navarro and Meyerhoff). The study conducted in Germany (PMOS) included 16007 patients treated for an average of 7 days. The study conducted in the USA (ACES) included 18409 patients. Only the portion of these patients enrolled by June 2000

are included in this report. In the former (German) study, one patient was identified with a prolongation of the QT interval where the abnormality remained present after the drug was stopped.

A review by the sponsor of 28 non-serious and 27 serious clinical events showed no evidence of unexplained ventricular arrhythmias. Three sudden deaths were reported. In the latter (US) study, 127 (0.7%) patients reported serious AE's and 6 died. One of 129 ECGs showed new QT prolongation to 510 mSec.

The applicant concluded that there was no evidence for significant QT prolongation and no definite case of Moxifloxacin induced fatal cardiac events.

> *MO COMMENT: Insufficient ECGs were performed to address the incidence of QT prolongation.*

No new safety concerns were raised by the applicant regarding hepatic toxicity, photosensitivity or CNS events.

## Synopsis of Findings in "Spontaneous Adverse Event Reports"

Among the estimated 1,560,000 treated patients on record, one case of torsades de pointe was reported in an 83 year old woman treated in ICU with underlying heart disease, a pacemaker, hypokalemia and elevated serum digitalis (see section "Ventricular arrhythmias" below for further detail.)

Among all AE reports including spontaneous reports and those from post-marketing studies, the applicant identified 5 cases of Moxifloxacin related anaphylactic shock and 7 cases of anaphylactic reactions.
It was noted that 10 of these cases occurred shortly after the first dose and 2 after the second dose, which would be atypical for anaphylactic reactions without previous exposure. A direct histamine releasing reaction was considered unlikely since histamine release was not identified in dog studies during pre-clinical testing.

## ADRs Worldwide Reported in this Submission:

From the complete list provided by the applicant, the reviewer selected all ADRs of importance either because of unusual frequency, unusual severity or unusual character. These are summarized in the table on the next page.

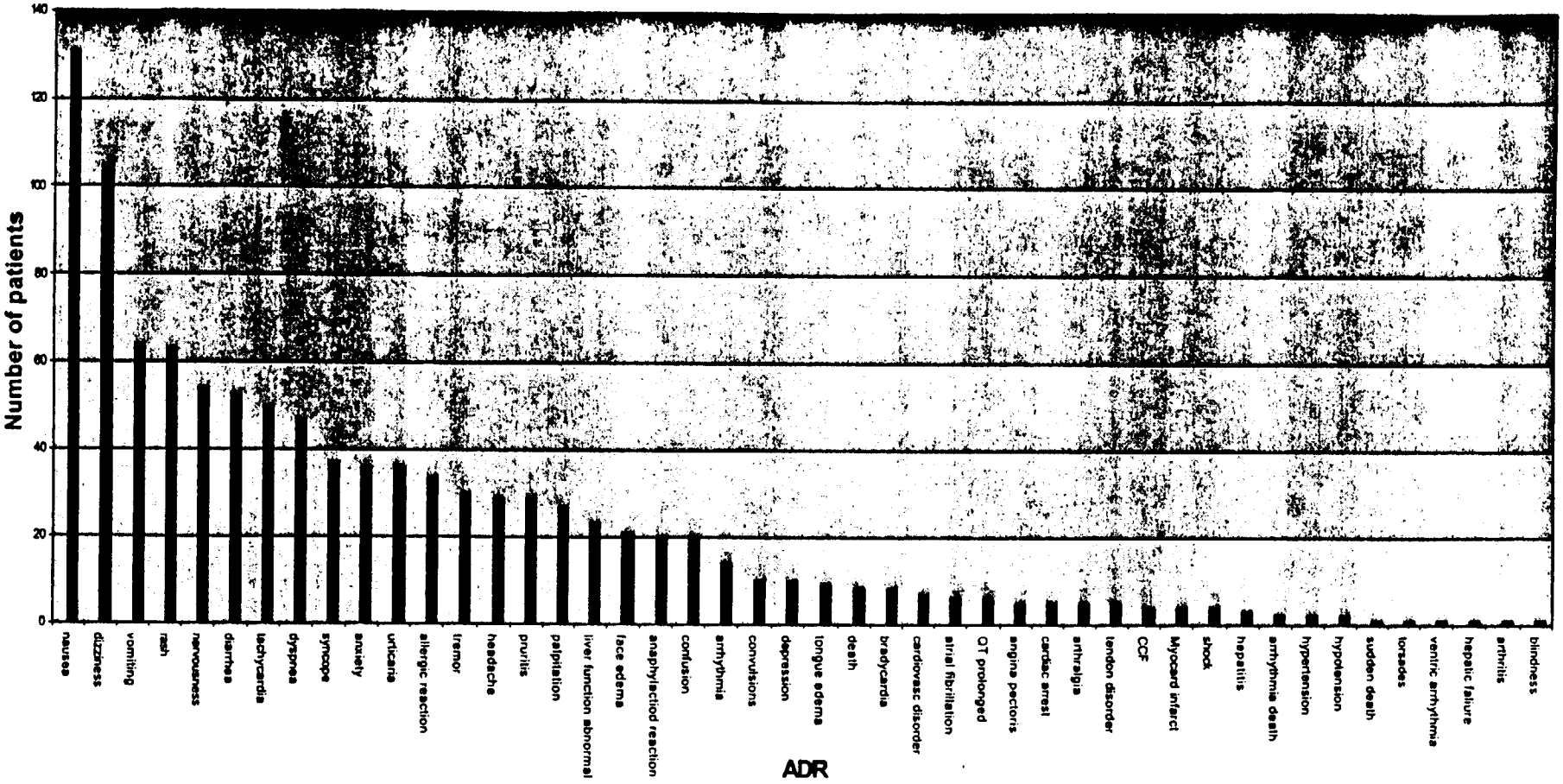
Table 19: All ADRs worldwide organized by body system. (Bold items are those conditions regarded by the reviewer as potentially related to prolongation of the QT interval)

| | **Spontaneous reports** | | **Literature** | **Post-marketing observational studies** | **Clinical phase I – IV studies** |
|---|---|---|---|---|---|
| | Serious | Non-serious | All | Serious | Serious |
| **Body as a whole** | | | | | |
| Allergic reaction | 24 | 8 | | 2 | |
| Face edema | 9 | 12 | | | |
| Anaphylactoid reaction | 19 | 1 | | | |
| Death | 5 | | | 3 | |
| Sudden death | 1 | | | | |
| **Cardiovascular** | | | | | |
| Angina pectoris | 4 | | | 1 | |
| **Arrhythmia** | 11 | 1 | | 2 | |
| **Arrhythmia death** | 1 | | | 1 | |
| Atrial fibrillation | 4 | | | 1 | 1 |
| Bradycardia | 4 | 1 | 1 | 2 | |
| Cardiovascular disorder | 2 | 4 | | 1 | |
| Congestive Cardiac Failure | 2 | | | | 2 |
| Cardiac arrest | 4 | 1? | | | |
| Hypertension | 2 | | | | |
| **Hypotension** | | 2 | | | |
| Myocardial infarct | 4 | | | | |
| **Palpitation** | 12 | 14 | | 1 | |
| **QT interval prolonged** | 3 | | | 2 | 1 |
| **Shock** | 4 | | | | |
| **Syncope** | 19 | 4 | | 8 | 6 |
| **Tachycardia** | 19 | 16 | | 12 | 3 |
| **Torsades** | 1 | | | | |
| **Ventricular arrhythmia** | 1 | | | | |
| **Ventricular fibrillation** | 2 | | | | |
| **Ventricular tachycardia** | 1 | | | | |

| | Spontaneous reports | | Literature | Post-marketing observational studies | Clinical phase I – IV studies |
|---|---|---|---|---|---|
| | Serious | Non-serious | All | Serious | Serious |
| **Gastrointestinal** | | | | | |
| Diarrhea | 7 | 35 | | 8 | 3 |
| Hepatitis* | 3 | | | | |
| Hepatic failure | 1 | | | | |
| Liver function tests abnormal | 8 | 10 | | 2 | 3 |
| Nausea | 8 | 118 | | 4 | 1 |
| Tongue edema | 4 | 2 | | 2 | 1 |
| Vomiting | 4 | 55 | | 4 | 1 |
| **Musculoskeletal** | | | | | |
| Arthralgia | | 5 | | | |
| Arthritis | 1 | | | | |
| Tendon disorder | 1 | 4 | | | |
| **Nervous system** | | | | | |
| Anxiety | 6 | 29 | | 1 | |
| Confusion | 6 | 14 | | | |
| Convulsions | 7 | | | 1 | 2 |
| Dizziness | 10 | 93 | | 1 | 1 |
| Headache | 2 | 27 | | | |
| Depression | 4 | 5 | | 1 | |
| Nervousness | 3 | 50 | | 1 | |
| Tremor | 2 | 26 | | | 2 |
| Blindness | 1 | | | | |
| **Respiratory** | | | | | |
| Dyspnea | 33 | 7 | | 4 | 3 |
| **Skin** | | | | | |
| Pruritis | 9 | 19 | | 1 | |
| Rash | 16 | 46 | | 1 | |
| Urticaria | 11 | 23 | | 1 | 1 |

*MO COMMENT: The frequency and the types of individual adverse events in this table reflect the known safety profile of Moxifloxacin. Most common are gastrointestinal complaints (nausea, vomiting) and minor neuropsychiatric complaints (dizziness, nervousness). Among the surrogate markers of possible arrhythmias from QT prolongation, most frequent were tachycardia, syncope, palpitation and arrhythmia. The specificity of each of these ADRs is low with respect to the possibility of Torsades de pointes. Taking into account the outpatient setting, and the malignant nature of this arrhythmia, true episodes of Torsades de pointe would be anticipated to result in syncope or sudden death rather than symptoms of tachycardia.*

A frequency distribution of all medically relevant adverse events was constructed by the reviewer to reflect a "safety fingerprint" for this drug as shown below in Fig 1.



Further characterization of individual ADRs

In addition to the individual line listings, some expanded patient narratives were presented in this submission, apparently selected on the basis of relevance to the question of anaphylaxis, ventricular arrhythmias, and hepatic reactions. The criteria for selection of these reports are not provided.

A synopsis of cases identified by the medical reviewer from the line listings as medically "relevant" is provided below.

## Anaphylaxis and Anaphylactoid Reaction

Serious allergic reactions were described in 7 patients during the first reporting period and 36 patients during the second reporting period. The mean age of the patients was 47 years (range 20-87). Of those with data available, there were 6 males and 14 females, the mean interval between start of therapy and the ADR was 1.7 days (range 0-7). Where the outcome was known, resolution occurred in 15 and a life-threatening response was recorded in 6.

> *MO COMMENT: The unusual character of this adverse event, affecting a wide range of age groups is highly suggestive of a drug-related effect. Taking into account the under-reporting anticipated from a study of this sort, the incidence of serious anaphylactic reactions is unlikely to be less than 43/1,560,000 (28 per million) among patient taking moxifloxacin.*

The applicant provided narratives for the following seven cases, representative of anaphylactic reactions in the database.

Table 20:
Narratives selected by the applicant for patients with anaphylactic reactions ("?" indicates data not provided)

| Age/sex | Indication | Time to event | Signs and symptoms | Other drugs | Outcome |
|---|---|---|---|---|---|
| 41/F | Sinusitis | 45 min | Swelling of extremities & throat, dizziness, rash | primidone | Resolved |
| 26/f | Sinusitis | 15 min | "Anaphylactoid reaction" BP 50/30 | ? | Resolved |
| 32/M | Bronchitis | Minutes | Anaphylactic shock, itching, swelling, dyspnea, BP100/60 | [redacted] | Hospitalization |
| ?/F | ? | 30 min | Anaphylactic shock, dyspnea, "BP drop to 80" | ? | Recovered |
| 34/F | Bronchitis | 10 min | Weakness, rash, swelling of face and | [redacted] | Reversed |

| Age/sex | Indication | Time to event | Signs and symptoms | Other drugs | Outcome |
|---|---|---|---|---|---|
| | | | body | | |
| 68/M | Bronchitis | 20 min | Nausea, urticaria, circulatory collapse | [redacted] | Recovered |
| 75/F | Asthma+ infection | 2hr | Urticaria edema hypotension | [redacted] | Recovered |

## Cardiovascular Events

Based on the data provided, the reviewer concluded that many of the cardiac events were unrelated to QT prolongation and were probably not related to moxifloxacin. They included angina (3 cases), irregular heartbeat (2), atrial fibrillation (3), AV block (1), bradycardia (4), cardioavascular dysregulation (1), circulatory problems (1), hypertension (5), hypotension (8), myocardial infarction (3), palpitations (15), and tachycardia (20).

Ventricular fibrillation was reported in a 69 year old female and a 45 year old male. Neither case description was adequate to determine attributability.

### 1) Cardiac arrest

This was reported in 4 patients as detailed below.

Table 21: Cardiac arrest ("?" indicates data not provided)

| Patient # | Age/sex | Meds | Underlying disease | Days to AE | Suspected etiology | Reversed |
|---|---|---|---|---|---|---|
| 200002333 See under torsades | | | | | | |
| 200001964 | 69/F | [redacted] furosemide, warfarin | LBBB, atrial fibrillation | 4 | Underlying heart disease | Recovered |
| 200006482 | 50/M | ? | Alcoholism, NIDDM | 3 | Convulsion | Died |
| 200006651 | 40/F | Prednisone | ? | 2 | Arrhythmia | Died ** |

***MO COMMENT: Very limited data are available on this young patient. Given the age and absence of known confounding factors, a fatal arrhythmia due to moxofloxacin cannot be excluded.*

### 2) QT prolongation

Three such cases were reported, but no electrocardiographic data was provided.
Table 22: QT prolongation ("?" indicates data not provided)

| Patient # | Age/sex | Meds | Underlying disease | Days to AE | Suspected etiology | Reversed |
|---|---|---|---|---|---|---|
| 200000138 | ? | ? | ? anaphylactic shock | ? | ? (no ECG data) | ? |
| 200003338 | ? | ? | ? | ? | From monitor (no ECG data) | ? |
| 200006230 | ? | ? | Cardiomyopathy | ? | (no ECG data) | ? |

Two additional cases were reported where the QT prolongations were within "normal variation"

**3) Syncope:**

Syncope was reported in 37 patients. Vasovagal reactions, a viral infection and CNS disease were presumed in some of the cases. The individual patient data provided were insufficient to characterize the etiology of these cases, many of which were reported to be mild, such as "feeling faint".

> *MO COMMENT: The cases of syncope, while compatible with a drug induced arrhythmia, could equally be attributed to a legion of other causes. In isolation, this small number of cases does not constitute a compelling signal for cardiotoxicity.*

**4) Ventricular arrhythmias**

a) *Torsades de pointes*:

Case # 200000233. This was an 83 year old female with sick sinus syndrome, a pacemaker, coronary heart disease, and cardiac failure. Admitted for pneumonia, this patient was found to have a low potassium (value not given) high digoxin levels and a QT interval of 490mS. During hospitalization she had a convulsion and cardiac arrest with successful resuscitation. On day 4 of moxifloxacin therapy, the QT interval was 510 mS followed by an episode of Torsades de Pointe (TdP), which was terminated with electro-conversion.

> *MO COMMENT: The contribution of moxifloxacin to the TdP in this heavily confounded case is unclear. In the absence of any other documented cases of TdP in this large database, this single case does not constitute a significant signal for moxifloxacin induced TdP.*

b) Ventricular extrasystoles

Two cases were described, one of "increased ventricular extrasystoles" and one of "intermittent spontaneous arrhythmia" beginning on days 4 and 3 of treatment with Moxifloxacin respectively. Both persisted at least several days beyond the time that the medication was stopped. ECG data was not provided.

c) Ventricular fibrillation

A single case described as "flutter/fibrillation" was discovered during investigation of the patient's exertional dyspnoea. Upon review of the medical records by the attending physician, no evidence of ventricular fibrillation was found

**5) Sudden deaths**

Nine reported sudden deaths are reflected in the table below.

Table 23: Sudden deaths (9 cases) - "?" indicates data not provided

| Patient # | Age/sex | Meds | Underlying disease | Days to AE | Suspected etiology | Reversed |
|---|---|---|---|---|---|---|
| 200001041 | ?40/? | ? | ? | 2 | Arrythmia | Died* |
| 200001397 | 25/F | [redacted] | Menstrual bleeding | 3 | Found dead at her TV | Died** |
| 200001501 | 77/M | Theophyllin | Pneumonia, pacemaker | 3 | ? | Died |
| 200001822 | 81/M | [redacted] | MI, Atherosclerosis | 7 | ?CVA or cardiac cause | Died |
| 200001960 | 82/F | [redacted] | Hypertension depression | 1 | ? | Died |
| 200004270 | 61/M | ? | Diabetic renal failure | ? | Diabetic complications | Died |
| 200004356 | 88/F | ? | Hypertension | 1 | pneumonia | Died |
| 200006810 | 70/M | Nifedipine, digoxin, [redacted] | NIDDM HT atrial fibrillation | 1 | ? cardiac disease according to physician | Died |
| 200002106 | 81/M | Cipro, [redacted] | Atrial fibrillation, cardiac failure, HT | 1 | "malignant rhythm disorder"- no documentation | Died |

*MO COMMENT:*

** The medwatch form that appears to correspond with this patient (#200001573BWH) describes a 40 year old female given Avelox and prednisone for bronchitis on June 1 2000. On June 2, the patient was admitted to the hospital with "arrhythmias". The patient died of a cardiac arrest on the following day. An autopsy was normal. There was no previous cardiac history. The applicant states that attempts by Bayer to obtain additional information from the physician were unsuccessful.*

***While a drug related arrhythmia cannot be excluded in this patient, the clinical notes include a history of a concurrent gynecological problem, menorrhagia and a related anemia, lassitude and a temperature of 39 °C. Moxifloxacin was prescribed for the presence of rales in the chest. These features raise the possibility of a septic abortion/pelvic thrombophlebitis and emboli as a cause of death in this young female.*

## FDA Update on Spontaneous Reporting

Results of the above report of Avelox® use in 1.5 million patients showed that *torsades de pointes* was observed to occur in one patient in this database. On 27 March 2001, the applicant reported to the Division that Avelox® had been used in 5 million patients worldwide. In an attempt to update safety information on signal cardiac events, the Adverse Events Reporting System (AERS) database was searched by the medical officer on 27 April 2001. There were three episodes of *torsades de pointes*. This updated rate of 3 events/5 million (1/1.7 million) is consistent with the observation reported by the applicant in the SPUR.

## Hepatotoxicity

A summary of patients identified from the line listings with hepatic disorders is given below.

Table 24: Patients with possible hepatotoxicity ("?" indicates data not provided)

| Patient # | Age/sex | Meds | Underlying disease | Days to AE | AE | Reversed |
|---|---|---|---|---|---|---|
| 9909866 | ?/M | ? | MI | 2 | Transaminase ↑ | Improved |
| 9910476 | 71/M | ? | ? | 1 | LFT↑ | R |
| 20000552 | ? | ? | ? | ? | Cholestatic hepatitis (LFTs not provided) | ? |
| 200003941 | ? | ? | ? | ? | Possible liver failure in a chronic alcoholic | ? |
| 2000036043902 | ? | ? | ? | ? | Liver dysfunction with elevated liver enzymes | ? |

20 additional cases of "liver function tests abnormal" are recorded.

*MO COMMENT: Given the scant description of these cases, the drug attributablilty cannot be determined. Numerically there does not appear to be an excess of putative hepatotoxicity over and above that anticipated as background in a database this size.*

## Hemolysis and Blood Dyscrasias

Three diverse cases of hematological abnormalities listed respectively as "low platelets and Hb", "suspected paroxysmal nocturnal hemoglobinurea" and "pancytopenia" do not suggest a specific drug related toxicity.

## Nervous System

Miscellaneous adverse events related to the nervous system were reported. Included were 4 cases of depression, 3 of grand mal convulsions, and 4 cases of paralysis or paresis where Guillaine Barre Syndrome was suspected in 2.

*MO COMMENT:*

*Despite the large numbers of exposures to moxifloxacin in this report, the data suffer from several deficiencies.*

1) *Based on a comparison of the solicited ADRs in observational studies and the unsolicited ADRs in spontaneous adverse event reports, it appears the considerable under-reporting has occurred in the bulk of patients providing the safety information.*
2) *The line listings provided scant information. In many instances, not even the age and sex of the patient or the outcome of the event are known. In the absence of additional information regarding underlying conditions and concomitant medications, drug attributability cannot be determined.*
3) *Duplications of data are possible due to more than one AE being reported for a given patient. The sponsor has not identified these duplications.*
4) *Drug utilization is presumptive based on sales and distribution. The number of patients who actually received drug may be overestimated.*

*The relative frequencies of most medically relevant adverse events appear consistent with those recognized in the original NDA. "Anaphylactoid reactions" are a new category of serious AEs that have emerged in this post marketing study and must be addressed in a revision of the label.*

*Reports that may be related to cardiotoxicity are difficult to interpret given the paucity of clinical information. Two unexplained deaths in young patients raise suspicions of a fatal arrhythmia but in the absence of further clinical information this remains speculative. Three cases of alleged QT prolongation and one of ventricular fibrillation were not substantiated by data.*

## Medical Officer's Conclusions and Recommendations

Taking into account the limitations of this report, additional labeling should be provided to address the anaphylactoid reactions described. While new cardiac concerns have not been identified, the existing concerns of cardiac safety remain. The reviewer regards the safety of Moxifloxacin as reflected in this report as sufficient to support approval for the indication of uncomplicated skin and skin structure infections with suitable labeling regarding anaphylactoid reactions.

## Conclusions/Recommendations

The applicant fulfilled all of the Phase IV requirements that were stipulated in the approval letter from December 1999. The data generaterd from these studies were able to expand the safety database of moxifloxacin, and demonstrated that there was no increased mortality associated when used according to the approved dosage and frequency of administration. The recommendation is for approval of moxifloxacin for the treatment of uncomplicated skin and skin structure infections.

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# Appendix A

## CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA:** | 21-334 |
| **Submission Date:** | 10/26/00 |
| **Drug:** | Moxifloxacin hydrochloride (Avelox®) oral tablets |
| **Sponsor:** | Bayer Corporation<br>West Haven, CT |
| **Type of Submission:** | New NDA<br>(Resubmission of USSSI Indication from NDA 21-085) |
| **OCPB Reviewer:** | Joette M. Meyer, Pharm.D. |

## I. BACKGROUND

Moxifloxacin (BAY 12-8039) is a synthetic C-8-methoxy-fluoroquinolone antibiotic. The oral formulation was approved in the United States on December 10, 1999 for three indications: acute sinusitis; acute bacterial exacerbations of chronic bronchitis; and community-acquired pneumonia. A fourth indication of skin and skin structure infections was deemed "approvable" pending the results of Phase IV studies.

Section 6 of NDA 21-334 contains three pharmacokinetic/pharmacodynamic studies performed as Phase IV commitments for NDA 21-085 (moxifloxacin oral tablets).

## II. INDICATION AND DOSAGE

The applicant is seeking approval of moxifloxacin 400 mg once daily for 7 days for the treatment of skin and skin structure infections.

## III. CLINICAL PHARMACOLOGY SYNOPSIS

**What is the effect of age and gender on the pharmacokinetic parameters of moxifloxacin, in terms of $AUC_{0-12}$ and $C_{max}$ after a 400 mg single oral dose?**

**Age**

- The $AUC_{0-12}$ of moxifloxacin was not statistically different across age groups (young, middle aged, and elderly), after adjustment for body weight.
- The $C_{max}$ of moxifloxacin was statistically lower between young (2.96 mg/L) and middle aged (2.90 mg/L) and elderly (3.21 mg/L) subjects. When normalized to body weight, the difference between young subjects and the other two age groups persisted (0.54, 0.58, and 0.58 kg/L, respectively).

**Gender**

- Females had a 30% higher $AUC_{0-12}$ and a 34% higher $C_{max}$ than males, which was statistically significant. This difference was lower, but persisted after adjustment for body weight (12% and 15% higher for $AUC_{0-12}$ and $C_{max}$, respectively).

[redacted]

**What is the duration of QTc prolongation obtained with moxifloxacin (1) after single escalating doses up to 3-times the approved dose, (2) compared to levofloxacin and erythromycin after doses up to 2-times the approved dose, and (3) compared to sparfloxacin after single doses and dosing to steady state?**

Moxifloxacin-induced changes in QTc are summarized in the following table. Data on the comparator drugs (sparfloxacin, levofloxacin, and erythromycin) are

also included for comparison. Changes in QTc are reported at the time of $C_{max}$ (i.e., $T_{max}$) and at the time of maximum QTc during a 12 hour interval. For reference, the approved dose of moxifloxacin is 400 mg, levofloxacin 500 mg, and erythromcyin 500 mg. Sparfloxacin is approved as a 400 mg loading dose, followed by 200 mg.

**Summary of Changes in QTc Parameter by Drug and Dose**

| Drug | Dose | ΔQTc* at $C_{max}$ (msec) | Max ΔQTc#^ (msec) |
|---|---|---|---|
| Moxifloxacin | 400 mg – single dose | 9.3 – 11.9 (100267)<br>9.2 – 16.9 (100263)<br>5.3 – 10.6 (100264) | 26.0 – 28.6 (100267)<br>23.6 – 28.4 (100263)<br>25.3 – 30.9 (100264) |
| | 400 mg – multiple dose | 14.0 – 19.6 | 32.6 – 38.2 |
| | 800 mg | 17.4 – 20.9 (100267)<br>16.3 – 19.5 (100263) | 36.2 – 37.0 (100267)<br>28.3 – 31.5 (100263) |
| | 1200 mg | 30.2 – 35.7 | 42.1 – 45.8 |
| Sparfloxacin | 400 mg – single dose | 12.9 – 20.2 | 30.6 – 35.8 |
| | 200 mg – multiple dose | 21.5 – 27.0 | 36.9 – 42.4 |
| Levofloxacin | 500 mg | 2.1 – 6.4 | 19.3 – 22.2 |
| | 1000 mg | 7.3 – 11.8 | 20.8 – 21.7 |
| Erythromycin | 1000 mg | 2.2 – 6.3 | 19.6 – 20.8 |

* range of change using all four definitions of baseline
\# range of change using three definitions of baseline
^ Corresponding max ΔQTc on placebo is 16.0-20.2 msec (100263 and 100267)

- The regression equation for moxifloxacin was determined by compiling data from all three studies (see figure below): $\Delta QTc = 2.18 + 2.80C_{max}$

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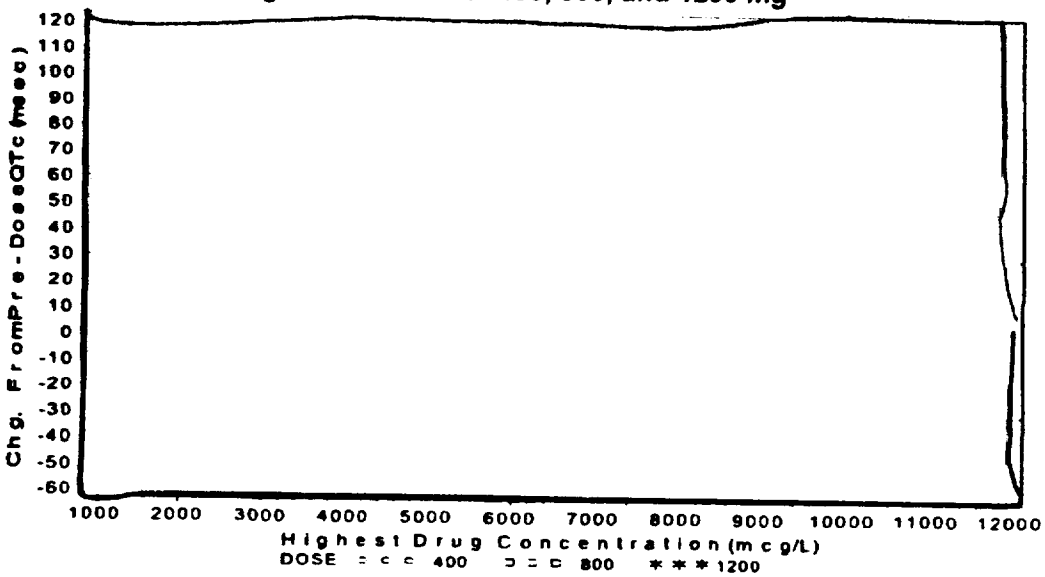
**ΔQTc versus Individuals' $C_{max}$ of Moxifloxacin Following Single Oral Doses of 400, 800, and 1200 mg**




## IV. RECOMMENDATION

The information contained in Item 6: Human Pharmacokinetics and Bioavailability of NDA 21-334 for moxifloxacin oral tablets has been reviewed and was found to be acceptable and adequate to support approval.

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) _____

cc: HFD-590: /NDA 21-334
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ