

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-085

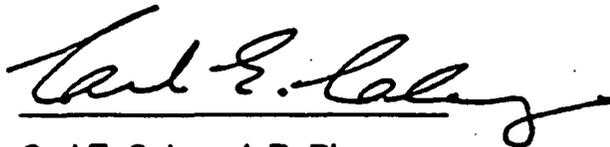
ADMINISTRATIVE DOCUMENTS

Section 13: The following information is hereby provided pursuant to 21 U.S.C. 355(b) and 21 C.F.R. 314.53:

Patent Number: 4,990,517
Expiration Date: 30 June 2009
Type of Patent: drug, drug product and method of use
Name of patent owner: Bayer AG
Agent: applicant (Bayer Corporation) has a place of business in the U.S.

Patent Number: 5,607,942
Expiration Date: 4 March 2014
Type of Patent: drug, drug product and method of use
Name of patent owner: Bayer AG
Agent: applicant (Bayer Corporation) has a place of business in the U.S.

The undersigned declares that Patent Nos. 4,990,517 and 5,607,942 each cover the formulation, composition, and/or method of use of moxifloxacin. This product is the subject of this application for which approval is being sought.



Carl E. Calcagni, R. Ph.
Vice President, Regulatory Affairs
Pharmaceutical Division
Bayer Corporation

EXCLUSIVITY SUMMARY FOR NDA # 21-085 SUPPL # _____

Trade Name AveloxTM Generic Name moxifloxacin HCl

Applicant Name Bayer HFD # 590

Approval Date If Known 12/10/99

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES // NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO //

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES // NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain: N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain: N/A

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

 N/A

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES / ___ / ! NO / ___ / Explain: N/A

!
!

Investigation #2 !

IND # _____ YES / ___ / ! NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES / ___ / Explain _____ ! NO / ___ / Explain N/A

!

Investigation #2 !

YES / ___ / Explain _____ ! NO / ___ / Explain N/A

!

!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

 / S / 7.11/15/99
Signature Date
Title: Project Manager

 / S / 12/22/99
Signature of Office/ Date
Division Director

cc: Original NDA

Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21085 Trade Name: AVELOX (MOXIFLOXACIN HCL)

Supplement Number: Generic Name: MOXIFLOXACIN HCL

Supplement Type: Dosage Form: TAB

Regulatory Action: PN Proposed Indication: Community Acquired Pneumonia
Acute Exacerbation of Chronic Bronchitis
Sinusitis

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?
 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, VALERIE JENSEN

Signature U /S/ Date 11/9/99

Pediatric Waiver Request:

Bayer hereby requests a waiver from the conduct of pediatric studies for this NDA. Cartilage lesions have been demonstrated in the weight bearing joints of immature dogs given moxifloxacin. This is a class effect of quinolones. The Warnings section of the proposed package insert cautions against the use of this product in pediatric patients and in adolescents (less than 18 years of age).

Although Bayer Corp. does not believe this effect translates itself into human pathology, Bayer believes that it is necessary to get additional experience on moxifloxacin in adults prior to performing pediatric studies.

**APPEARS THIS WAY
ON ORIGINAL**

Section 16 - Debarment Certification:

Bayer hereby certifies under FD&C Act Section 306 (k)(1) that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

One investigator who participated in study protocol D96-024 (see section 8 of this NDA) has been restricted in the use of investigational products as of January 26, 1998. He is Dr. Thomas B. Edwards (Albany, NY) and he was the principal investigator for Center 30 of D96-024. Dr. Edwards was not debarred or restricted at the time his services were rendered to Bayer. However, the data generated by Dr. Edwards for this study have been entirely deleted and therefore no analysis of this study include Dr. Edwards data.

**APPEARS THIS WAY
ON ORIGINAL**

**MEMORANDUM**

DATE: December 10, 1999

TO: NDA 21-085

FROM: Mark J. Goldberger M.D., M.F.H. /S/
Division Director
Division of Special Pathogen and Immunologic Drug Products

SUBJECT: Division Director's memo for Avelox™

Efficacy:

I agree with the overall assessment of the review team including that expressed by Dr. Hopkins in his Team Leader memo. Based upon in vitro data moxifloxacin has the potential to show enhanced activity against both gram + organisms and anaerobes however this has not been apparent to date in the information submitted by Bayer. The ultimate usefulness of this drug will probably depend upon Bayer performing additional clinical trials to assess the drug's activity in such settings and of course the results of such trials. The absence of cytochrome 3A4 interactions and once daily doses are also benefits.

Safety:

The toxicity issues associated with this product are obviously of concern. There is no question that there is a positive exposure Q-T prolongation relationship. Information to easily assess the clinical significance of quantitative changes in Q-T is not readily available for this as well as other products. We believe that the risk of serious clinical events with the degree of prolongation that we have seen with moxifloxacin particularly given the absence of pharmacokinetic interactions to be very low but probably not zero. Although we are indebted to the Division of Cardio-Renal drug Products for their help in assessing this situation, we do not necessarily agree with their conclusion that any degree of Q-T prolongation absent added benefit for a drug should automatically lead either to a non-approval or an approval as a second line agent. Ultimately the degree of risk is likely to be related to the exposure Q-T relationship, pharmacokinetic factors and perhaps other considerations such as tissue penetration etc. Furthermore antimicrobial therapy is not generally administered in situations in which the choice is between the drug in question and no therapy. Rather the choice is between one therapy or an alternative therapy. For the toxicity under discussion; Q-T prolongation with the risk of torsades and given other toxicities of antimicrobial therapy, it is not clear that at least some alternative antimicrobials would not offer similar level of risk.

It should be noted that during the review, concerns regarding the potential hepatotoxicity of this product were identified. Review of case records however indicated that for the two patients in question who presented with significant elevations of both bilirubin and transaminases there were convincing explanations in terms of concomitant illness. Both this issue and that of the Q-T prolongation are well covered in Dr. Sack's safety review.

Postmarket requirements:

I think that it is important to note that both by [REDACTED] requiring the agreed upon Phase IV commitments we believe that we have improved the risk benefit for approval of this product. The additional studies that Bayer will perform will also provide the opportunity to gain additional information to evaluate the safety profile of moxifloxacin and to better understand the relationship between Q-T prolongation and likely clinical effects. The review of the IV formulation of moxifloxacin will also provide an additional venue to evaluate these matters.

**APPEARS THIS WAY
ON ORIGINAL**

Team Leader's Memorandum

TO: NDA 21-085

FROM: Robert Hopkins MD, MPH & TM

RE: AVELOX (oral tablet) NDA

DATE: December 10, 1999

The objectives of this memorandum are to:

- addresses the rationale for waiving pediatric exclusivity for this application
- outline the risk-benefit evaluation for the [] proposed indications including a description of the recommendations provided in the consult provided by the Division of Cardio-renal Drug Products

PEDIATRIC EXCLUSIVITY WAIVER

The sponsor has asked for a waiver from the conduct of pediatric studies for this NDA. This is based on the cartilage lesions that have been demonstrated in the weight bearing joints of immature dogs given moxifloxacin. Although the sponsor does not believe that this effect translates itself to human pathology, the sponsor believes that it is necessary to get additional experience with moxifloxacin in adults prior to performing pediatric studies.

CFR 314.55 (c) (2) discusses the reasons why a full waiver should be granted. Three reasons are provided in this section:

- (i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.
- (ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed.
- (iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

Among the three indications recommended for approval in adults (mild to moderate community acquired pneumonia, acute bacterial sinusitis, acute exacerbation of chronic bronchitis), both mild to moderate community acquired pneumonia and bacterial sinusitis are indications where there would not be a meaningful therapeutic benefit over existing therapies in pediatric populations. The low numbers of pediatric patients with AECB precludes the need to develop data for these indications.

In addition, the potential for arthropathy, torsade de point, and arrhythmic events raises additional concerns that preclude the need to perform additional pediatric studies for these approved adult indications.

RISK BENEFIT ANALYSIS

The risk benefit assessment for moxifloxacin is an excellent example where there is the need to balance a mild to modest benefit for many patients (millions of exposed patients) with the potential for a serious risk of a potentially life threatening adverse event from the drug (torsade de point and sudden death) for a few patients.

It is my opinion that the benefit of moxifloxacin for the three proposed respiratory indications (mild to moderate community acquired pneumonia, acute bacterial sinusitis, and acute exacerbation of chronic bronchitis) out weighs the risks associated with the use of this product. The benefits for each of the [redacted] proposed indications have been detailed in each of the MO efficacy reviews. These reviews have found that moxifloxacin demonstrated equivalence to comparator agents when used at the recommended doses and duration (Drs. Meyerhoff, Mann, and Powers) and risks have been articulated in the MO safety review (Dr. Leonard Sacks). This assessment differs from the advice provided by the Division of Cardio-Renal Drug products. The conclusions from this consult was that it is "hard to justify approving this agent as first line therapy for non life threatening infections in which there are a plethora of treatment choices". It goes further to state: "While drugs that prolong the QT are not automatically disapproved, it is generally required for such drugs to demonstrate additional benefits compared to other in the same class (or drugs for the same indication) that do not have this adverse effect. If there is a quinolone that provides similar efficacy but does not prolong the QTc (or cause any other serious toxicity not seen with moxifloxacin), it would be difficult to recommend the approval of moxifloxacin."

Because of the differences in opinion could potentially exist regarding the need to "demonstrate additional benefits", the application was brought before the Anti-Infective Advisory Committee on October 21st, 1999. The committee voted 10 of 10 (in favor) that the drug has demonstrated efficacy for the [redacted] proposed indications. In contrast, the committee voted 7 of 10 (in favor) that the drug has demonstrated safety for the [redacted] proposed indications proposed. It should be stated, however, that the committee did not vote on the risk-benefit of each indication as the questions were originally stated.

It was clear that there were reservations by some of the Committee members regarding the safety of the product related to the drug's ability to prolong the QT interval in a dose dependent manner. It was also clear that the Committee did not see any clear advantage (benefit) of the moxifloxacin over other drugs used to treat similar indications. Hence, the general statement that it is necessary to demonstrate "additional benefit" for a new drug associated with mild QTc prolongation (without clinical events) was not adhered to by the Committee.

In contrast to my recommendation for approval of the three proposed respiratory indications [redacted]

[redacted] If post marking data suggest that QTc prolongation for moxifloxacin is not associated with arrhythmic events or sudden death, the benefits for this population may outweigh the risks (See Recommendations below). To date, I am not aware of any other country that has approved moxifloxacin for this indication.

The sponsor has proposed the following risk-benefit analysis in support of the use of moxifloxacin independent of each specific indication. My comments qualify these statements:

- **Broader spectrum of coverage**

Comment: The broad spectrum of moxifloxacin is clearly an advantage of moxifloxacin. However, this characteristic is not unique to this drug. Levofloxacin, for example, also has broad spectrum activity and has been shown to be well tolerated among the [redacted] [redacted] prescriptions world wide (Anti-Infective AC meeting 10/20/99). Furthermore, to date, the drug has not been studied in a large number of indications (such as intra-abdominal infections and nosocomial pneumonia) of varied severity supporting broad spectrum coverage that is clinically relevant.

- **Superior resistance characteristics**

Comment: Recognized bug drug combinations that are deemed to be of emerging clinical relevance include penicillin resistant *S. pneumoniae*, vancomycin resistant enterococci, [redacted] resistant *S. aureus* and gram negative organisms that have extended spectrum beta-lactamase activity. In this application, there were no or very limited data supporting the use of moxifloxacin for these pathogens. Although, moxifloxacin has good in vitro activity against *S. pneumoniae*, the clinical data supporting its activity against this pathogen is very limited for the two indications where PRSP isolates were collected (See acute sinusitis and community acquired pneumonia review).

- **Short duration, once daily therapy**

Comment: This is clearly an advantage for moxifloxacin, although these properties are not unique to this drug. For example, azithromycin is recommended for 5 days once daily for acute exacerbation of chronic bronchitis. In contrast, levofloxacin is used once daily, however, for 7 days.

- **No dose adjustments**

Comment: This is true for patients with renally impaired patients. However, patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) have not been studied. In addition, the pharmacokinetics of moxifloxacin in patients with moderate and severe hepatic insufficiency (Child Pugh Classes B and C) have not been adequately studied.

- **No CYP 450 interaction**

Comment: The data describing a lack of a CYP 450 interaction is reviewed in detail in the clinical pharmacology review (Dr. Joette Meyer). Of particular concern is the potential for an interaction with the CYP 450 3A4 enzyme. Moxifloxacin does not act as a substrate or inhibitor of this enzyme. Given the potential for since there are a number of other drugs that can either act a substrates or block this enzyme The sponsor correctly states that this was not demonstrated for moxifloxacin.

- **No liver, CNS, phototoxicity**

Comment: The fact that was no clear signal for liver or CNS toxicity for moxifloxacin in the NDA database does not preclude rare but severe hepatic and CNS events during the post marketing period. In fact, the incidence and severity of hepatic toxicity associated with trovafloxacin was not appreciated until well after approval. This was also the case with lomefloxacin and ofloxacin with regard to CNS toxicity. Phototoxicity for moxifloxacin was not demonstrated using a number of animal species and only 2 of almost 5,000 exposed patients developed a reversible mild rash with administration of moxifloxacin during the clinical trials (See safety review, Dr. Leonard Sacks).

- **Favorable morbidity and mortality trends**

Comment: The sponsor performed and submitted a number of post-hoc morbidity and mortality analyses on October 7, 1999. These were again presented at the October 21, 1999 advisory committee meeting.

Mortality

A variety of different populations were evaluated when performing these analyses: populations in controlled studies vs. both controlled and uncontrolled studies, populations with death occurring at different times during the study, populations being studied for a variety of indications or combination of indications, and populations included in studies/study arms that evaluated a variety of different doses. The sponsor stated the "primary population" was the group of controlled studies using the 400 mg dose vs. the pool of control groups. This analysis was reproduced along with a family of other analyses using different definitions of the "primary population" and using death defined regardless of attribution to study drug or failure of study drug (death due to infection progression). The p-values for these analyses are shown below and the rates are shown on the following two pages. These additional retrospective analyses confirm that the differences in death rates between moxifloxacin and comparator agents is not significant when using the safety population regardless of how the analyses were conducted. This involved changing the time at which deaths were counted in relation to treatment, the dose of moxifloxacin, the indication for treatment, or the inclusion of controlled vs. all studies in the analysis. Death rates were "significantly lower" ($P < 0.05$) for only 8 of the analyses among the 64 analyses conducted. Six of these counted deaths within 30 days following treatment and five involved analyses that included only controlled studies. Seven were in analyses that excluded the 200 mg dose indicating the many of the moxifloxacin deaths rates were in patients who received this lower dose. The sponsor decided to highlight the mortality rates that occurred within 30 days of treatment among controlled studies only for patients who were treated for any indication (),

CAP + AECEB, or CAP alone. For these three analyses, the p values were 0.056, 0.009, and 0.045, respectively using the Asymptotic calculation. Although these analyses reach statistical significance when not adjusting for multiple comparisons, the asymptotic calculation should only be used when the number of deaths in either treatment arm are 5 or more. In these analyses, the number of moxifloxacin deaths were 7, 5, and 4, when evaluating [redacted] CAP + AECEB, or CAP alone, respectively. Not shown in their analyses were the p-values when using the Exact calculation (a more appropriate statistical test). Using this statistical test the p-values were 0.58, 0.039, and 0.17, respectively, for these populations.

**APPEARS THIS WAY
ON ORIGINAL**

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"Significant" Deaths Rates Across Studies

Timing of deaths/Type of Studies	Controlled Only		Controlled and Uncontrolled	
	Moxi vs Control	Moxi 400 vs Control	Moxi vs Control	Moxi 400 vs Control
All Deaths				
Safety Pop	0.836	0.425	0.736	0.375
[REDACTED]				
CAP	0.524	0.278	0.768	0.17
Deaths within 30 days				
Safety Pop	0.417	0.146	0.398	0.155
[REDACTED]				
CAP	0.161	0.046	0.327	0.037
Deaths within 14 days				
Safety Pop	0.435	0.121	0.446	0.15
[REDACTED]				
CAP	0.241	0.071	0.452	0.062
Deaths on Treatment				
Safety Pop	0.848	0.926	0.966	0.805
[REDACTED]				
CAP	0.487	0.56	0.487	0.749

Deaths: Controlled Studies

Population	All Moxi Doses			Moxi 400 mg			Moxi 200 mg			Control		
	n	N	%	n	N	%	n	N	%	n	N	%

All Deaths

Safety Pop	20	4301	0.47	14	3745	0.37	6	556	1.1	17	3415	0.5
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CAP	14	968	1.6	8	701	1	6	267	2.3	13	705	1.8
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Deaths within 30 days from the end of Treatment

Safety Pop	14	4301	0.33	9	3745	0.24	5	556	0.9	15	3415	0.44
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CAP	9	968	1.14	4	701	0.57	5	267	1.87	12	705	1.7
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Deaths within 14 days from the end of Treatment

Safety Pop	12	4301	0.28	7	3745	0.19	5	556	0.9	13	3415	0.38
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CAP	9	968	1.14	4	701	0.57	5	267	1.87	11	705	0.16
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Deaths on Treatment

Safety Pop	3	4301	0.07	2	3745	0.05	1	556	0.18	2	3415	0.06
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CAP	3	968	0.31	2	701	0.29	1	267	0.37	1	705	0.14
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Deaths in Both Controlled and Uncontrolled Studies

Population	All Moxi Doses			Moxi 400 mg			Moxi 200 mg			Control		
	n	N	%	n	N	%	n	N	%	n	N	%

All Deaths

Safety Pop	22	4926	0.45	16	4370	0.37	6	556	1.1	17	3415	0.5
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CAP	16	968	1.68	10	955	1.05	6	267	2.3	13	705	1.84
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Deaths within 30 days from the end of Treatment

Safety Pop	16	4926	0.32	11	4370	0.25	5	556	0.9	15	3415	0.44
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CAP	11	968	0.93	6	955	0.63	5	267	1.9	12	705	1.7
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Deaths within 14 days from the end of Treatment

Safety Pop	14	4926	0.28	9	4370	0.21	5	556	1.1	13	3415	0.38
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CAP	11	968	0.93	6	955	0.06	5	267	1.9	11	705	1.56
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Deaths on Treatment

Safety Pop	3	4926	0.06	2	4370	0.05	1	556	0.18	2	3415	0.06
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CAP	3	968	0.31	2	955	0.21	1	267	0.37	1	705	0.14
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Hospitalization

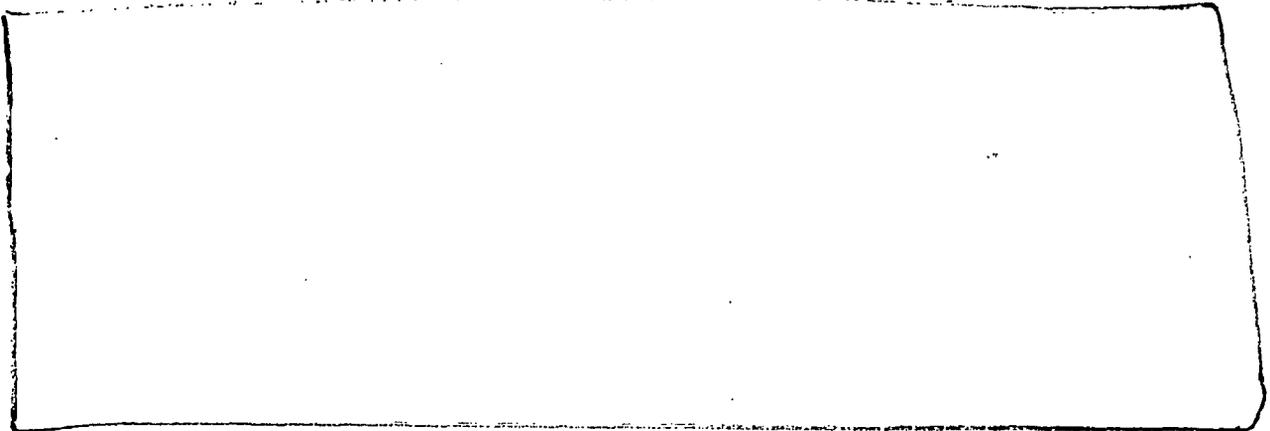
The sponsor summarized hospitalization or prolongation of hospitalization for all studies since these were an option for an action taken as the result of an adverse event. Three events were considered to be related to the initial disease: (COSTART terms) "bronchitis", "pneumonia", and "lung disorder". The sponsor stated that the hospitalization rates were significantly lower for bronchitis, pneumonia, lung disorder, and a combination of all. Their results of this analysis are shown below:

Adverse Events	Moxifloxacin 400 mg (N=1925)	Control (N=1629)
Bronchitis	1 (0.05%)	4 (0.25%)
Pneumonia	13 (0.68%)	13 (0.8%)
Lung Disorder	4 (0.21%)	15 (0.92%)
Any of the Above	18 (0.94%)	31 (1.84%)

Because these analyses were provided late in the review process, it was not possible to validate them as was done for the mortality analyses. The retrospective nature of the analyses precludes drawing any conclusions regarding the superiority of moxifloxacin over control agents. Like the comparable death rates in the safety population as previously described, these analyses do provide some assurance that hospitalization may not be worse with moxifloxacin as compared with controls and are interesting hypothesis generating findings that could be pursued in prospectively designed studies.

RECOMMENDATIONS

1. The respiratory indication should be approved if the sponsor is willing to conduct a number of phase 4 studies as indicated below and include appropriate labeling cautioning patients and health care workers regarding the potential risks associated with QTc prolongation. Appropriate wording should be included in the WARNINGS, PRECAUTIONS (Information for Patients), and a new section should be added to the label that further educates the patient on the risk of QT prolongation. The specific wording that should be included in the label is presented below. To reduce the probability that moxifloxacin will be used inappropriately, this kind of labeling is an important part of the risk management for the drug following approval. Although this new section of the label is not common for other antimicrobial products, it has been recently used for the drug Tamiflu to improve its appropriate use.





PROPOSED LABELING

WARNINGS

MOXIFLOXACIN HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. THE DRUG SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA AND PATIENTS RECEIVING CLASS IA (E.G. QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G. AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS, DUE TO THE LACK OF CLINICAL EXPERIENCE WITH THE DRUG IN THESE PATIENT POPULATIONS.

Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded, therefore moxifloxacin should be used with caution when given concurrently with these drugs.

The effect of moxifloxacin on patients with congenital prolongation of the QT interval has not been studied, however, it is expected that these individuals may be more susceptible to drug-induced QT prolongation. Because of limited clinical experience, moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia.

The magnitude of QT prolongation may increase with increasing concentrations of the drug, therefore the recommended dose should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. In 787 patients with paired valid ECGs in Phase III clinical trials, the mean \pm SD effect of moxifloxacin 400 mg on the QTc interval was 6 ± 26 msec. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 4000 patients, however certain predisposing conditions may increase the risk for ventricular arrhythmias.

PRECAUTIONS

Information for Patients:

To assure safe and effective use of moxifloxacin, the following information and instructions should be communicated to the patient when appropriate:

Patients should be advised:

- ◆ that moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- ◆ that moxifloxacin should be avoided in patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents.
- ◆ that moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- ◆ to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.

PATIENT INFORMATION

The following section should be added to the end of the label to further educate patients.

Bayer Logo
Name & Address

Patient Information About:

AVELOX™

(moxifloxacin hydrochloride)
400 mg Tablets

This section contains important information about AVELOX (moxifloxacin hydrochloride), and should be read completely before you begin treatment. This section does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of AVELOX. The medicine described here can be prescribed only by a licensed health care professional. If you have any questions about AVELOX talk with your health care professional. Only your health care professional can determine if AVELOX is right for you.

What is AVELOX?

AVELOX is an antibiotic used to treat lung or sinus infections caused by certain germs called bacteria. AVELOX kills many of the types of bacteria that can infect the lungs and sinuses and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). AVELOX, like all other antibiotics, does not kill viruses.

You should contact your doctor if you think your condition is not improving while taking AVELOX. AVELOX Tablets are red and contain 400 mg of active drug.

How and when should I take AVELOX?

AVELOX should be taken once a day for 5 or 10 days depending on your prescription. It should be swallowed and may be taken with or without food. Try to take the tablet at the same time each day.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of AVELOX even if you missed a dose by mistake. You should not take a double dose.

Who should not take AVELOX?

You should not take AVELOX if you have ever had a severe allergic reaction to any of the group of antibiotics known as "quinolones" such as ciprofloxacin or levofloxacin.

You should avoid AVELOX if you have a rare condition known as congenital prolongation of the QT interval. If you or any of your family members have this condition you should inform your health care professional. You should avoid AVELOX if you are being treated for heart rhythm disturbances with certain medicines such as quinidine, procainamide, amiodarone or sotalol. Inform your health care professional if you are taking a heart rhythm drug.

You should also avoid AVELOX if the amount of potassium in your blood is low. Low potassium can sometimes be caused by medicines called diuretics such as furosemide and hydrochlorothiazide. If you are taking a diuretic medicine you should speak with your health care professional.

If you are pregnant or planning to become pregnant while taking AVELOX, talk to your doctor before taking this medication. AVELOX is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

AVELOX is not recommended for children.

What are the possible side effects of AVELOX?

AVELOX is generally well tolerated. The most common side effects caused by AVELOX, which are usually mild, include nausea, vomiting, stomach pain, diarrhea, dizziness and headache. You should be careful about driving or operating machinery until you are sure AVELOX is not causing dizziness. If you notice any side effects not mentioned in this section or you have any concerns about the side effects you are experiencing, please inform your health care professional.

In some people, AVELOX, as with some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. Although this has not caused any serious problems in more than 4000 patients who have already taken the medication, in theory it could result in extremely rare cases of abnormal heartbeat which may be dangerous. Contact your health care professional if you develop heart palpitations (fast beating), or have fainting spells.

Which medicines should not be used with AVELOX?

You should avoid taking AVELOX with certain medicines used to treat an abnormal heartbeat. These include quinidine, procainamide, amiodarone, and sotalol.

Some medicines also produce an effect on the electrocardiogram test, including cisapride, erythromycin, some antidepressants and some antipsychotic drugs. These may increase the risk of heart beat problems when taken with AVELOX. For this reason it is important to let your health care provider know all of the medicines that you are using.

Many antacids and multivitamins may interfere with the absorption of AVELOX and may prevent it from working properly. You should take AVELOX either 4 hours before or 8 hours after taking these products.

Remember

Take your dose of AVELOX once a day.

Complete the course of medication even if you are feeling better.

Keep this medication out of the reach of children.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.

PHASE 4 STUDIES

The Sponsor should commit to submitting the following data:

1. Post-marketing adverse event data following at least one million patient exposures worldwide should be submitted. A substantial proportion of these exposures will be from the United States. The results of this evaluation should be submitted to the Division by September 30, 2000.

Rationale: This data should provide added assurance that serious adverse events (including sudden death and torsade) does not occur at an event rate of [redacted] exposures as detected through a spontaneous collection system.

2. The sponsor should 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. The protocols and methods for this ongoing study should be submitted to the Division within ninety days of receipt of this letter. A report on this experience should be submitted to the Division by September 30, 2000.

Rationale: This study is currently ongoing in Germany and should be completed fairly quickly. Since the data is being collected in an active surveillance system (with the administration of questionnaires to physicians who prescribe the medication) it should provide more accurate information regarding the incidence of TdP or sudden death than a spontaneous surveillance system. Given the number of patients included, an event rate of more than [redacted] should be ruled out if no events are seen. [redacted]

3. The sponsor should 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.

Rationale: This study would provide additional information in US patients to study #2. Since the data will be collected in an active surveillance system it should provide more accurate information regarding the incidence of TdP or sudden death than a spontaneous surveillance system. Given the number of patients included, an event rate of more than [redacted] should be ruled out if no events are seen. [redacted]

However, it is felt that duplication of negative results found in the foreign active surveillance study is necessary as part of the overall risk assessment for moxifloxacin post approval.

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

Rationale: This study should provide additional information not contained in the NDA regarding the dose response of orally administered moxifloxacin when given at doses higher than what are currently recommended. It is felt that this is important since it is likely that some patients will receive higher doses (or exposures) of the drug during the post marketing period

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

Rationale: Since part of the risk assessment of moxifloxacin included a comparison of this drug to other drugs used for similar indications, the results of this study will provide valuable comparative information regarding the QTc prolonging effect of these agents at actual Cmax. This kind of information can only be obtained by conducting a cross over study. Ideally this should be conducted with drugs that are known to cause QTc prolongation (erythromycin) and drugs that are not thought to prolong the QTc interval and have not been associated with high rates of torsade and sudden death in the post marketing period (levofloxacin).

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

Rationale: Since it is not known if the QTc prolonging effect could be exacerbated by prolonged exposure, it is important to evaluate this effect at steady state. It is known that moxifloxacin accumulates by 30% following a 10 day daily dosing regimen. If factors such as potassium channels (or other factors) are sensitized by prolonged exposure to moxifloxacin, this study will serve to characterize this effect.

7. The sponsor should 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 should be submitted to the Division by December 31, 2000.

Rationale: It is important to characterize the effect of moxifloxacin and its major metabolites by gender and age. It is known that QTc effects are increased with other drugs in women (Ebert S, Liu X, Woosley R, J Women's Health 1998;7(5):547-57). This study should evaluate for these kind of potential differences.

— /S/

Robert Hopkins MD, MPH & TM
Medical Team Leader

Concurrence
HFD590/MTL/GoldbergerM