CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-277

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW OF NDA

NDA 21-277
AVELOX

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

Submission/Review Dates
Date of submission: November 4, 2000
Date review completed: September 24, 2001

Drug Identification

Generic name:	moxifloxacin (BAY 12-8039)
Proposed trade name:	Avelox
Pharmacologic category:	antimicrobial-fluoroquinolone
Route of administration:	intravenous

Regulatory materials reviewed
NDA 21-085, volumes 1.1-1.2, 1.269-1.298 and associated electronic files, submitted 12/9/98

[redacted]

NDA 20-596 (Raxar), MO review
NDA 20-677 (Zagam), MO review
Meeting minutes and handouts for meeting between Bayer and Division of Special Pathogens, May 1997
Correspondence between Bayer and Division of Special Pathogens from spring 1997 to autumn 2000

INTEGRATED REVIEW OF EFFICACY

Background
The oral formulation of Avelox (NDA 21-085) was approved December 10, 1999 for the indications community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), and acute sinusitis. A fourth indication, uncomplicated skin and skin structure infections, was approved April 27, 2001. The CAP indication is the only one for which there were studies performed with the intravenous formulation, and these studies provided the efficacy data for the application under review here (NDA 21-277). The plan of the sponsor was to demonstrate the efficacy of intravenous moxifloxacin for the treatment of CAP with a single North American study and demonstrate comparable bioavailability between the oral and iv formulations. These data would then support approval of the intravenous formulation for any indications already approved for the oral

formulation. In a May 1997 meeting, this strategy was discussed with the review division and found mutually agreeable. The sponsor was advised that failure to demonstrate efficacy of the intravenous formulation for the treatment of CAP and/or comparable bioavailability of the two formulations would put approval of the other indications at risk. At that meeting, the division also asked if other clinical trials were being conducted with the iv formulation, and Bayer acknowledged that there was a European CAP study with the same design as the North American one, but with amoxi-clavulanate as the comparator. Bayer added that they intended to use the data from the European study as supportive for organisms and safety.

In August 1997 and October 1998, the MO received and reviewed 2 different phase III protocols for intravenous moxifloxacin for CAP. The study described in the August '97 protocol used ceftriaxone/cefuroxime as comparator, the study described in the October '98 protocol used trovafloxacin as comparator. The trial that used ceftriaxone/cefuroxime (August '97 submission) was cancelled prior to enrollment because of Bayer's concerns about the review division's view of an unapproved comparator (cefuroxime). In July 1999, Bayer changed the comparator in the October '98 protocol to levofloxacin because of safety concerns with trovafloxacin.

In August 1999, the MO requested clarification from Bayer regarding the number of trials being planned for iv moxifloxacin for CAP. In an email dated Aug 16, 1999, Bayer informed the division that the 'Trovan study' (#100039, for which levofloxacin had been substituted as the comparator) 'is still the only one trial for a moxifloxacin NDA.'

During summer and fall of 2000, there were a series of pre-NDA discussions with Bayer regarding several issues in the planned iv NDA. Records of the Oct 4, 2000 pre-NDA meeting mention study #200036, an open label, ex-US study using amoxicillin-clavulanate as comparator with clarithromycin added at investigator's discretion. It appeared that this study was a source of resistant pneumococcal isolates.

NDA 21-277 was submitted in November 2000. Early review of the submission to determine fileability identified CAP studies #100039 and #200036 showed that the sponsor identified these studies as pivotal. The study report for #200036 documented the start of that study in February 1999, 6 months before Bayer's August 1999 statement that #100039 was the only trial in the moxifloxacin iv NDA.

Clinical efficacy of moxifloxacin iv in CAP

Review of the documents and correspondence described above suggests that the sponsor elected to include this second CAP study in NDA 21-277 some time after August 1999. The use of data from additional studies to provide information on resistant isolates can be a means of supplementing the database for drug efficacy against resistant pneumococcal isolates, which are notoriously difficult to identify in clinical specimens. The review division has recognized this difficulty, and the MO has viewed the results of study #200036 as a potential source of additional information about moxifloxacin efficacy in the treatment of penicillin-resistant *S. pneumoniae* (PRSP) infections. It should be pointed out, however, that as an open label study, #200036 does not provide the same

level of evidence for efficacy as would a prospective double-blinded, randomized, controlled study such as #100039. For these reasons, #200036 was regarded by the reviewing MO as a possible source of PRSP isolates. Because of the difference in design, possibility of bias, and lower level of evidence provided by the data from #200036, efficacy data from this study were analyzed separately. Tables 1 and 2 below summarize efficacy results across various populations for each study.

Table 1. Clinical response at TOC for Study 100039

Valid for Efficacy	All stratum	Moxifloxacin Control 95% CI (Mantel-Haenszel) 95% CI (Normal approx.)	157/182 (86%) 161/180 (89%) (-8.9%, 4.2%) (-10.5%, 4.1%)
	Severe stratum	Moxifloxacin Control 95% CI (Normal approx.)	48/61 (78.7%) 39/49 (79.6%) (-16.2%, 14.4%)*
Valid for Safety	All stratum	Moxifloxacin Control 95% CI (Mantel-Haenszel) 95% CI (Normal approx.)	168/249 (67%) 173/258 (67%) (-7.5%, 8.7%) (-8.1%, 9.0%)
	Severe stratum	Moxifloxacin Control 95% CI (Normal approx.)	48/83 (57.8%)* 41/75 (54.7%)* (-12.3%,18.7%)*
Microbiologically Valid for efficacy valid patients	All stratum	Moxifloxacin Control 95% CI (Mantel-Haenszel) 95% CI (Normal approx.)	66/80 (83%) 70/78 (90%) (-17.2%, 4.1%)* (-18.0%, 3.5%)*
	Severe stratum	Moxifloxacin Control 95% CI (Normal approx.)	24/31 (77.4%)* 20/24 (83.3%)* (-26.9%, 15.0%)*

* Calculated by the biostatistics reviewer.

Table 2: Clinical response for Study 200036.

Per protocol at TOC visit	All stratum	Moxifloxacin Control 95% CI	241/258 (93.4%) 239/280 (85.4%) (2.91 %, 13.19%)
	Severe stratum	Moxifloxacin Control 95% CI	119/129 (92.2%) 116/137 (84.7%) (0.0%, 15.2%)*
Per protocol at visit 21-28 days post therapy	All stratum	Moxifloxacin Control 95% CI	216/258 (83.7%) 208/280 (74.3%) (2.60%, 16.27%)
	Severe stratum	Moxifloxacin Control 95% CI	105/129 (81.4%) 97/137 (70.8%) (0.4%, 20.7%)*
Valid for Safety ITT at visit 21-28 days post therapy	All stratum	Moxifloxacin Control 95% CI	220/301 (73.1%) 209/321 (65.1%) (1.63%, 15.96%)
	Severe stratum	Moxifloxacin Control 95% CI	108/158 (68.4%) 98/163 (60.1%) (-2.2%, 18,7%)*
Microbiologically Valid at follow-up	All stratum	Moxifloxacin Control 95% CI	56/64 (87.5%) 53/71 (74.6%) (-0.21%, 25.91%)
	Severe stratum	Moxifloxacin Control 95% CI	32/37 (86.5%) 31/40 (77.5%) (-8.0%, 26.0%)*

* Calculated by the reviewer.

Inspection of Tables 1 and 2 shows consistently different results between the double-blinded study (#100039) and the open label study (#200036). Efficacy rates are generally similar across treatment groups in study #100039, with the exception of certain subpopulations (eg. microbiologically valid) where moxifloxacin efficacy is slightly lower than control. In study #200036, point estimates of efficacy rates for moxifloxacin are consistently about 10 points higher than those reported for control.

Revisiting the data in NDA 21-085 describing the efficacy of oral moxifloxacin for the treatment of CAP provides another means of assessing the data from study #200036. Table 3 below presents clinical efficacy in CAP for oral moxifloxacin compared with oral high-dose amoxicillin or clarithromycin, similar comparators to those used in study #200036.

Table 3. Clinical efficacy CAP due to *S. pneumoniae*: oral formulations

	Moxifloxacin 400 mg po q D	Control*
All CAP studies	80/89 (90%)	67/75 (89%)

*Control = amoxicillin 1000 mg po tid or clarithromycin 500mg po bid

Inspection of Table 3 shows that for the treatment of CAP, the results for oral moxifloxacin and comparator are similar to what was observed in intravenous study #100039. Efficacy rates are similar for the two treatment groups across most populations. The open-label design of study #200036 and the different pattern of efficacy data when compared with study #100039 or with results from the CAP studies in the NDA for the oral formulation makes the results of #200036 less central to the review of drug efficacy.

Results from study #100039 support the demonstration of efficacy of intravenous moxifloxacin in a manner consistent with what was observed for the oral formulation of the drug, except that there appears to be slightly lower efficacy for moxifloxacin among microbiologically evaluable patients with severe CAP. The results from study #200036 do not refute this overall finding of clinical efficacy for intravenous moxifloxacin in CAP.

Efficacy in patients with *S. pneumoniae* bacteremia

The evaluation of efficacy for intravenous moxifloxacin warrants consideration of those patients with more severe disease than would be treated with an oral formulation. As noted in table 1 above, there is a suggestion of somewhat lower efficacy rates for moxifloxacin than comparator in the subpopulation of microbiologically evaluable patients with severe disease. The MO analyzed data from patients with pneumococcal bacteremia as a means of better understanding the efficacy of intravenous moxifloxacin in this subpopulation. Patients with CAP and pneumococcal bacteremia are important to the understanding of drug efficacy for two reasons: 1) they represent the 'gold standard' of diagnostic criteria for pneumococcal pneumonia, and 2) they represent a category of severe disease for which the demonstration of drug efficacy is critical. Patients with pneumococcal pneumonia and bacteremia have a substantially higher mortality than those with pneumococcal infection confined to the lung.

Table 4 presents a summary of clinical efficacy rates in patients with pneumococcal bacteremia across all controlled, double-blinded studies of oral or intravenous moxifloxacin.

Table 4. Clinical efficacy in CAP patients with *S. pneumoniae* bacteremia from all controlled, double-blinded studies of oral or intravenous moxifloxacin

Study	**Moxifloxacin 400 mg**	**Control**
ORAL MOXIFLOXACIN		
Study 0119	1/1 (100%)	1/1 (100%)*
Study 0140	6/9 (67%)	10/10 (100%)**
INTRAVENOUS MOXIFLOXACIN		
Study 100039	9/10 (90%)	11/11 (100%)***
TOTAL	**16/20 (80%)**	**22/22 (100%)**

*Clarithromycin
**High dose amoxicillin
***Trovafloxacin or levofloxacin

Review of Table 4 shows that efficacy of moxifloxacin demonstrated in controlled, double-blinded trials of patients with CAP and pneumococcal bacteremia is markedly lower than efficacy observed with control agents. Penicillin or amoxicillin have long been drugs of choice for the treatment of pneumococcal infections. The increasing importance of penicillin resistance among clinical isolates of *S. pneumoniae* suggests that the effectiveness of these drugs may be waning. A drug that can be considered an adequate replacement for these agents should demonstrate comparable efficacy.

Efficacy in CAP due to penicillin-resistant *S. pneumoniae* (PRSP)
The data presented in Table 4 are important to the consideration of both moxifloxacin efficacy in the treatment of severe pneumococcal infections and efficacy in resistant pneumococcal infections. Consideration of a claim for efficacy in the treatment of infections due to PRSP warrants that efficacy in the treatment of pneumococcal infections due to susceptible strains be well characterized. As noted above, Table 4 raises issues regarding moxifloxacin success rates in patients with bacteremia, one of the most serious complications of pneumococcal pneumonia.

At the time of the submission of the NDA for oral moxifloxacin, the sponsor requested a claim for efficacy in the treatment of CAP due to PRSP. This was not approved for two reasons. One reason was that the small body of data regarding efficacy in bacteremic patients suggested low rates for moxifloxacin (Table 4, study 0140). The other was that there was a very small number of resistant pneumococcal isolates, and moxifloxacin efficacy observed in these infections was lower than was seen in pneumococcal infections in general. Table 5 below revisits these data, and demonstrates that, while sample sizes were extremely small, some question was raised regarding moxifloxacin efficacy in infections due to PRSP.

Table 5. Clinical efficacy of oral moxifloxacin in CAP: *S. pneumoniae* and PRSP

	Moxifloxacin 400 mg po q D	Control
CAP due to *S. pneumoniae* (all isolates)	80/89 (90%)	67/75 (89%)
CAP due to PRSP	6/8 (75%)	3/3 (100%)

For the purpose of reconsidering the claim for efficacy of moxifloxacin in CAP due to PRSP, the sponsor combined all PRSP isolates from studies of both the oral and intravenous formulations in US and ex-US studies. Those isolates identified in the US studies were tested for penicillin susceptibility using both e-test and broth dilution. All of these isolates met the criterion for penicillin resistance (MIC$\geq$ 2.0 mcg/ml) when tested using broth dilution, the standard criterion that defines penicillin resistance. Clinical efficacy for patients from whom this small number of organisms was isolated was observed to be 100%.

There were also PRSP isolates identified in ex-US studies. In these studies, only the e-test was used to assess penicillin resistance. Because 6 of the 7 isolates identified in these studies had MIC values by e-test $\leq$ 2.0 mcg/ml and were not tested by the reference method (broth dilution), they are not regarded as meeting the criteria of penicillin resistant. As has been noted in the Microbiology review, values obtained by the e-test method can differ from those obtained with the reference method by one dilution, and are therefore not reliable indicators of penicillin resistance for review purposes. There was one patient in the ex-US population with a PRSP isolate with a PCN MIC 6.0 mcg/ml by e-test(patient 10674/study 140) who may be regarded as having been infected with PRSP. This patient was a clinical failure.

Additional data from a study of oral moxifloxacin (#100224) were submitted in the four-month safety update. This study provided an additional six patients from whom a PRSP isolate was cultured and tested by both e-test and broth dilution. All six of these patients were clinical cures. Thus the total database from patients with CAP provides 13 PRSP isolates with a clinical cure rate of 12/13 (92.3%). These results are summarized below in Table 6.

Table 6. Clinical efficacy in patients with CAP due to PRSP

Study/Patient No.	Isolate	PCN MIC Etest	PCN MIC broth	Clinical response
100039(iv)/13007	*S. pneumoniae*	3.0	2.0	Resolution
100039(iv)/13025	*S. pneumoniae*	4.0	4.0	Resolution
100039(iv)/48013	*S. pneumoniae*	1.5	2.0	Resolution
100039(iv)/71001	*S. pneumoniae*	3.0	4.0	Resolution
D96-025(po)/4006	*S. pneumoniae*	2.0	2.0	Resolution
D96-026 (po)/248	*S. pneumoniae*	4.0	4.0	Resolution
140 (po)/10674	*S. pneumoniae*	6.0	-	Failure
100224 (po)/1012	*S. pneumoniae*	3.0	2.0	Resolution
100224 (po)/1019	*S. pneumoniae*	8.0	4.0	Resolution
100224 (po)/1028	*S. pneumoniae*	3.0	4.0	Resolution
100224 (po)/1032	*S. pneumoniae*	1.5	2.0	Resolution
100224 (po)/604001	*S. pneumoniae*	2.0	2.0	Resolution
100224 (po)/614002	*S. pneumoniae*	1.0	2.0	Resolution

The data presented regarding clinical efficacy of moxifloxacin in patients with CAP and pneumococcal bacteremia suggest that moxifloxacin is less effective than comparator agents. These data raise questions regarding the appropriateness of this drug for the treatment of severe pneumococcal pneumonia. With such questions outstanding, it would be premature to recommend approval of claims for efficacy in the treatment of pneumonia due to PRSP.

Efficacy in sinusitis due to penicillin-resistant *S. pneumoniae* (PRSP)

The sponsor has also submitted data to support a claim for efficacy of moxifloxacin in the treatment of patients with sinusitis due to PRSP. These data were submitted following discussions with the sponsor in which it was established that if a claim for PRSP in sinusitis were sought, it would be necessary to show efficacy for PRSP in CAP as well. Data supporting drug efficacy in more serious resistant pneumococcal infections is warranted prior to the consideration of a resistance claim for a less serious infections. By pooling data from 3 oral and 2 intravenous studies of moxifloxacin in sinusitis, the sponsors provided data on 13 patients infected with PRSP. Overall efficacy observed for this population was 11/13 (85%). The sponsor has begun to accrue a database characterizing moxifloxacin efficacy in resistant pneumococcal infections, however questions raised about drug efficacy in patients with pneumococcal bacteremia suggest that this issue be addressed prior to approving any resistance claims.

Conclusion

Questions raised about drug efficacy in patients with pneumococcal bacteremia who received oral moxifloxacin arise again in patients who received the intravenous formulation. This is an important component of the evaluation of drug efficacy for any intravenous formulation, and the results presented here do not adequately establish efficacy in this subpopulation of seriously ill patients with pneumococcal pneumonia. Similar questions are raised by the observation of lower efficacy rates for moxifloxacin in the subpopulation of patients with severe CAP who were microbiologically evaluable. These findings call into question the approvability of intravenous moxifloxacin for CAP, and suggest that consideration of resistance claims can only occur after moxifloxacin efficacy in serious pneumococcal infection has been established.

Andrea Meyerhoff MD MSc DTMH
Medical Officer

Medical Officer's Addendum Review of NDA

NDA 21-277
Avelox

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

Submission/Review Dates
Date of Submission of Major Amendment: October 31, 2001
Date review completed: November 30, 2001

Drug Identification

Generic name:	moxifloxacin (BAY 12-8039)
Proposed Trade Name:	Avelox
Pharmacologic category:	antimicrobial-fluoroquinolone
Route of administration:	intravenous

Regulatory materials reviewed
NDA 21-085 (Avelox PO) MO, Statistical, and Microbiological Reviews for CAP and AECB
NDA 21-277 (Avelox IV) Associated electronic files, MO, Statistical, Microbiological Reviews
NDA 20-634 SE1-008 and NDA 20-635 SE1-007 (Levaquin), MO and Statistical Review
FDA Anti-infectives Advisory Committee Meeting slides (December 1, 1999)
Moxifloxacin Clinical Efficacy
FDA Anti-infectives advisory committee meeting slides (May 16, 2001)
Telithromycin Drug-Resistant *S. Pneumoniae*

The major amendment submission (October 31, 2001) consisted of
1) Age breakdown and patient ID numbers for the drug-related cardiac adverse events in the NDA studies (100039 and 200036)
2) Additional information available on the cardiac SAEs in the ongoing, double-blind moxifloxacin IV studies (Random code was provided under separate cover)
3) MedWatch Forms for the cardiac SAEs from open-label moxifloxacin I. V. trails
4) An age breakdown for the cardiac SAEs from ongoing, open-label moxifloxacin IV studies
5) A breakdown of the COSTART events for pneumonia patients under age 65 from the post-marketing safety database for moxifloxacin tablets.

EXECUTIVE SUMMARY

The original medical reviewer for this NDA application had determined that a safety issue hindered the approval of this application. The safety issue was the discrepancy in the numbers of ventricular tachycardia cases between the moxifloxacin arm (5 cases) verses the control arm (1 case) in the pooled safety database of studies 100039 and 200036. In challenge of this conclusion, the applicant submitted a major amendment just prior to the action date of November 2nd, 2001, which extended the clock by 1 month. I was asked to review this major amendment submission in the context of the whole NDA application, and provide an addendum review with recommendations regarding:

1) Cardiac safety issue
2) Four additional organisms (penicillin-resistant *S. pneumoniae, S aureus, K pneumoniae*, and *L. pneumophilia*) which the applicant was seeking claim with this NDA
3) Appropriate Labeling if the product can be approved

Cardiac Safety Issue

The 5 to 1 discrepancy of ventricular tachycardia (V-tach) represented all V-tach cases reported. A close scrutiny of each of the cases in consultation with CDER's cardiorenal division, revealed the following. One of the V-tach cases in the moxifloxacin arm was miscoded. EKG review showed atrial flutter and not V-tach. Another case from the moxifloxacin was a case of bigeminy and not V-tach. Of the remaining three cases of V-tach, 2 events occurred on study drug therapy and 1 occurred 9 days after IV and 2 days after oral study drug therapy. Non of the V-tach cases were associated with prolonged QT duration and there was a satisfactory alternate explanation for the development of V-tach in each of the cases. Only one of the cases may be considered to have a run of polymorphic V-tach, the rest being monomorphic. Thus, the number discrepancy between the two arms existed but whether it was a difference of 5 to1 verses 3 to 1 was up to interpretation. Furthermore, the evidence for V-tach in relationship to QT prolongation was not strong in these cases based on what is currently known regarding the patho-mechanism of fluoroquinolones and QT prolongation. What was not disputable was that all the five cases in the moxifloxacin arm was that the patients were elderly (>64 years of age).

The applicant submitted in their major amendment a table entitled "drug-related cardiovascular events" to show that the overall treatment emergent cardiovascular adverse events were similar for the two arms (4.5% moxifloxacin verses 4.7% control). However, analysis of the numbers revealed that these comparable adverse event rates was a washout effect of increased cardiac events in the moxifloxacin arm (which included rhythm disturbances as well as ECG abnormalities including QT prolongation) versus increased vascular events in the control arm (which were mainly phlebitis).

Table 1 : Incidence Of Drug-Related Cardiovascular Adverse Events From IV Moxifloxacin NDA Safety Data Pool: All Patients

Adverse Event	All Bay 12-8039 (N=550)	Control (N=579)
Any Event	25 pts (4.5%)	27 pts(4.7%)
	Total No. Events = 31	Total No. Events = 30
Cardiac Rhythm/EKG Abnormalities	N=18 (72% of TNE)	N=6 (20% of TNE)
	n=15 patients	n=6 patients
QT Interval Prolonged	6 (1.1%)	2 (0.3%)
Ventricular Tachycardia	4 (0.7%)	0 (0.0%)
Electrocardiogram Abnormal (ST-T wave Changes)	3 (0.5%)	0 (0.0%)
Tachycardia	2 (0.4%)	1 (0.2%)
Atrial Fibrillation	1 (0.2%)	1 (0.2%)
Supraventricular Tachycardia	1 (0.2%)	0 (0.0%)
Ventricular Extrasystoles	1 (0.2%)	0 (0.0%)
Arrhythmia	0 (0.0%)	2 (0.3%)
Vascular Abnormalities	N=7 (22.6% of TNE)	N=18 (60% of TNE)
	n=7 patients	n=18 patients
Phlebitis	4 (0.7%)	14 (2.4%)
Peripheral Edema	0 (0.0%)	2 (0.3%)
Vasodilatation	2 (0.4%)	0 (0.0%)
Deep Thrombophlebitis	0 (0.0%)	1 (0.2%)
Thrombophlebitis	1 (0.2%)	0 (0.0%)
Vascular Disorder	0 (0.0%)	1 (0.2%)
Other Cardiac-related Adverse Events	N=5 (16% of TNE)	N=5 (16.6% of TNE)
	n=5 patients	n=4 patients
Congestive Heart Failure	1 (0.2%)	0 (0.0%)
Myocardial Infarct	1 (0.2%)	0 (0.0%)
Palpitation	1 (0.2%)	0 (0.0%)
Pericardial Effusion	0 (0.0%)	1 (0.2%)
Pericarditis	0 (0.0%)	1 (0.2%)
Hypotension	2 (0.4%)	1 (0.2%)
Hypertension	0 (0.0%)	1 (0.2%)
Shock (septic)	0 (0.0%)	1 (0.2%)

Moreover, the actual discrepancy for increased ECG abnormalities/rhythm disturbances in the two arms lay in the elderly subgroup (>65 years of age; 12 patients or 15 events in the moxifloxacin arm verses 3 patients/events in the control arm). The pattern of the discrepancy in cardiac adverse event numbers between moxifloxacin treated group and the control group was apparent once again, and again in the elderly population. The following table shows the incidence of drug-related cardiovascular adverse events (age group $\geq$ 65 years).

Table 2: Incidence Of Cardiac Adverse Events From IV Moxifloxacin NDA Safety Data Pool by Age Group: Ages ≥ 65 years

Adverse Event	All Bay 12-8039 (N=248)	Control (N=243)
Any Event	16 patients (6.5%)	9 patients (3.7%)
	No. of Events = 19	No. of Events = 9
	(61.3% of TNE)	(30% of TNE)
Cardiac EKG/Rhythm Abnormalities	N=15 (48.4% of TNE)	N=3 (10% of TNE)
	n=12 patients	n=3 patients
Atrial Fibrillation	1 (0.4%)	0 (0.0%)
QT Interval Prolonged	4 (1.6%)	1 (0.4%)
Arrhythmia	0 (0.0%)	1 (0.4%)
Tachycardia	2 (0.8%)	1 (0.4%)
EKG abnormalities (ST-T wave changes)	3 (1.2%)	0 (0.0%)
Ventricular Tachycardia	3 (1.2%)	0 (0.0%)
Supraventricular Tachycardia	1 (0.4%)	0 (0.0%)
Ventricular Extrasystoles	1 (0.4%)	0 (0.0%)
Vascular Abnormalities	N=3 (9.7% of TNE)	N=5 (16.6% of TNE)
	n=3 patients	n=5 patients
Phlebitis	2 (0.8%)	3 (1.2%)
Peripheral Edema	0 (0.0%)	2 (0.8%)
Vasodilation	1 (0.4%)	0 (0.0%)
Other Cardiac-related Adverse Events	N=1 (3.2% of TNE)	N=1 (3.3% of TNE)
	n=1 patient	n=1 patient
Congestive Heart Failure	1 (0.4%)	0 (0.0%)
Shock (septic)	0 (0.0%)	1 (0.4%)

The applicant did submit additional serious cardiac adverse event data from their on-going intravenous Avelox protocols. However, due to the small numbers, this information did not provide a challenge to the pattern of increased cardiac events in the elderly population. It is important to also point out that although these increased cardiac adverse events were seen in the moxifloxacin arm, the overall mortality during treatment between the two arms was comparable.

In intravenous trials in community acquired pneumonia, 45% of moxifloxacin patients were greater than or equal to 65 years of age, and 24% were greater than or equal to 75 years of age. In 491 elderly (≥ 65 years) patients, ECG abnormalities (including ST-T wave changes, QT prolongation, Ventricular Tachycardia, Tachycardia, Atrial Fibrillation, Supraventricular Tachycardia, Ventricular Extrasystoles, and Arrhythmia) were reported in 4.8% of moxifloxacin patients (12/248) versus 1.2 % of comparator-treated patients (3/243). None of these

abnormalities was associated with a fatal outcome. During treatment, the overall mortality rate was 1% in moxifloxacin patients (3/248) versus 2% on comparator-treated patients (5/243).

Recommend

1) *Approval of the application with proper wording in the package insert to inform the physician/patient about the geriatric cardiac safety concern.*
2) *Phase IV commitment which includes 15-day safety reports of cardiovascular adverse events and a safety study in the elderly population that will disprove the geriatric cardiac safety concern, or confirm the concern and elucidate the reasons for the finding.*

Four additional organisms

Penicillin-resistant Streptococcus pneumoniae (PRSP)

The Levaquin application for PRSP has set a "threshold" for approval of other antibiotics seeking the PRSP claim (internal bi-divisional consensus: Divisions of Special Pathogen and Division of Anti-infective Drug Products). Thus, the PRSP data for Avelox through all CAP studies are summarized in the table below side-by-side with the Levaquin data that was used to grant approval for that drug.

Table 3: PRSP database for Levofloxacin and Moxifloxacin

	Levofloxacin Application		**Moxifloxacin Application**	
All CAP studies	8 studies total, 7 studies contributing PRSP organisms 4 randomized, 1 double-blind, only 1 PRSP isolate came from the double-blind study		7 studies total; 4 studies contributing PRSP organisms 5 randomized, 4 double-blind, 6 PRSP isolates coming from double-blind studies ** on-going Nosocomial Pneumonia study (a double-blind study) is contributing 6 PRSP isolates to this application (added later to the IV-Avelox NDA as part of 4 month safety update)**	
# Patients with *S. pneumoniae* CAP across all studies #cured/total (%response)	Levofloxacin **245/250 (98%)**	Control **39/41 (95%)**	Moxifloxacin Uncontrolled Studies 36/37 (97%) Controlled Studies 113/127 (89%) All Studies Total **149/164 (91%)**	Control 111/129 (86%) **111/129 (86%)**
# Patients with *S. pneumoniae* **bacteremia**	Levofloxacin **55/55 (100%)**		Moxifloxacin **30/34 (88%)**	Control **31/32 (97%)**
# Patients with PRSP across all CAP studies	Levofloxacin **15/15 (100%)** 15 evaluable of 18 total 11/15 "pivotal" meaning response evaluation during 5-21 day period post-Tx	Control 3/3 (100%) 3 evaluable of 4 total	Moxifloxacin **12/13 (92.3 %)** 13 evaluable of 19 total because E-test values between 1.5 to 2.0 µg/mL were excluded. Studies 140 and 20036 used E-test only. Clinical response date for all "resolved" cases were assessed between post-Tx days 10-36	Control 1/1 (100%) 1 evaluable of 6 total because E- test values were all 2 µg/mL and thus excluded
PRSP Patient Characteristics	Levofloxacin %total		Moxifloxain %total	
# Bacteremic	**6 6/15 (40%)**		**2 2/13 (15%)**	
# with Severe Dz	5 5/15 (33%)		6 6/13 (46%)	
# Hospitalized	9 9/15 (60%)		7/8 "resolved" 7/13 (54%)	

The total number of *S. pneumoniae* cases, the number of *S. pneumoniae* bacteremic cases, the number of PRSP cases, as well as the number of PRSP bacteremic cases all were less than the threshold set by the Levaquin application. In particular the number of patients who had a

successful outcome from PRSP bacteremia were too small (n=2). The applicant identified nineteen cases of PRSP across all moxifloxacin CAP studies plus 6 additional isolates from the ongoing Nosocomial Pneumonia Study (study 100024). Seven of these 19 isolates were only tested by the E-test method. Six of the seven had MICs of 1.5 to 2.0 ug/mL by E-test. Since the E-test may produce results that are one dilution different than those produced by the reference broth dilution method, these six isolates may not actually be penicillin-resistant. Therefore, only 13 PRSP cases were evaluable, of which 12 had the clinical outcome of "resolved". Even if we were to include all 19 PRSP isolates, the number of bacteremic patients stays the same at 2 patients. It is important to point out that although the numbers for each of the categories in the above table did not meet the threshold of Levaquin data, the patient population across all the studies actually had better control data with 4 double-blind studies in the moxifloxacin application versus only 1 double-blind study in the levofloxacin application. It should also be noted that the characteristics of bacteremia, severe disease, hospitalized are all used concurrently to arrive at the weight of the evidence. Thus, bacteremic cases do not necessarily imply severity of disease, but more the specificity of the diagnosis of true illness with the organism. Hence, although the current moxifloxacin application has less number of bacteremic cases, the numbers for the "severe" disease patients and "hospitalized" patients are more comparable with the Levaquin application. This information should be kept in mind in considering future actions if the claim for PRSP is re-submitted by the applicant with increased cases of *S. pneumoniae*, especially bacteremic *S. pneumoniae* cases by both penicillin-sensitive and resistant strains.

Legionella

The applicant presented data on 6 cases of Legionella across all CAP studies to date (from both PO and IV clinical trials). The applicant claims that all 6 cases resulted in a favorable clinical outcome and thus should be added to the list of organisms under the CAP indication. A closer scrutiny at the data however revealed the following. Only one patient had Legionella isolated in culture. The rest of the patients were by serology only. Urine antigen tests were also not available. Two of the patients were not considered to have severe disease with pneumonia (severity was defined using the ATS criteria). Furthermore three of the patients had S. pneumoniae isolated concurrently from their respiratory culture. Thus, it is hard to discern specificity of Legionella Pneumonia diagnosis for all of the 6 patients. At the present time, the number of Legionella cases, especially definitive cases, are not enough for this claim.

Staphylococcus aureus and Klebsiella pneumoniae

For these two organisms, there is enough number of cases to grant approval. The following is a summary of combining all isolates from the 6 CAP studies (4 studies for PO and 2 studies for IV). One of the PO studies was not a controlled study and thus the numbers for the comparator arm are less.

Table 4: Clinical Success Rates By Pathogen: CAP studies (6 studies Pooled)

	Moxifloxacin	Comparator
Staphylococcus aureus	21/25 (84%)	16/21 (76%)
Klebsiella pneumoniae	14/17 (82%)	9/13 (69%)

These two organisms had been approved in the Avelox PO NDA application under the indication Acute Exacerbation of Chronic Bronchitis. Now, with the combined numbers from all CAP studies, these two organisms should be granted approval for the CAP indication.

Recommend

1) *That the PRSP claim not be approved at this time. However it should be conveyed to the applicant that the moxifloxacin S. pneumoniae database is promising, and the totality of evidence within the context of the "threshold" will be reviewed if this claim for PRSP may be re-submitted in the future when more cases of S. pneumoniae, particularly bacteremic cases by both penicillin-sensitive and resistant strains are available.*
2) *That the Legionella claim not be approved at this time. Additional cases demonstrating disease from this organism are needed for approval (i.e. culture of the organism, serology plus urine antigen, no other culture positive, severe pneumonia, febrile)*
3) *That the claim for S. aureus and K. pneumoniae be granted for the indication of community-acquired pneumoniae.*

Labeling Specific Recommendations and Rationale

1) Because Biopharmaceutics has determined that the IV and PO formulations are not bioequivalent (Cmax is higher for IV), there is an increased safety concern with the IV formulation. If the label is to be a joint PO/IV package insert, then the geriatric cardiac safety concern should be articulated in the PRECAUTIONS, Geriatric Use and cross-references to the Geriatric Use section placed throughout the label (WARNINGS, INDICATION and USAGE, ADVERSE EVENTS, DOSAGE and ADMINISTRATION sections).

2) In the oral moxifloxacin application, only the mild/moderate stratum for CAP was approved. This was due in part to the lack of efficacy in the patients with *S. pneumoniae* bacteremia in comparison to the controls. In the IV trials, the efficacy in the patients with *S. pneumoniae* bacteremia is comparable to the control arm. Therefore, the request to expand the current CAP indication of mild/moderate CAP to mild/moderate/severe CAP is acceptable.

3) The clinical studies section should be reorganized and updated to show both PO and IV studies data with updated clinical response chart (which includes *S. aureus* and *K. pneumoniae*). It will be preferable to include descriptions of blinded controlled studies only in this section. However, if the applicant wants to include the results of the open-label IV European study (study 200036), there should be wording that states the comparator (IV amoxicillin/clavulanate) is not a FDA approved drug.

Signed: Rosemary Johann-Liang, M.D. Medical Officer, DSPIDP

Concurrences: Rigoberto Roca, M.D. Medical Team Leader, DSPIDP
Renata Albrecht, M.D. Acting Director, DSPIDP

CC: HFD-590/Original NDA #21-227
HFD-590/Division File
HFD-590/CSO/Ykong
HFD-590/Micro/Pdionne/Sbala
HFD-590/Tox/Aellis/Khastings
HFD-590/Chem/Dmatecka
HFD-590/Biopharm/JMeyer/FAjayi
HFD-590/Statistics/Qli/KHiggins

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Rosemary Johann-Liang
11/30/01 03:39:36 PM
MEDICAL OFFICER

Rigoberto Roca
11/30/01 06:24:37 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-277

CHEMISTRY REVIEW(S)

Chemistry Review Data Sheet

1. NDA 21-277

2. REVIEW #: 1

3. REVIEW DATE: 11/26/01

4. REVIEWER: Dorota Matecka

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	11/2/00
Amendment (BC)	5/8/01
Amendment (BC)	6/13/01
Amendment (AC)	7/3/01
Amendment (BC)	8/30/01
IR letter	11/19/01
Amendment (BC)	11/20/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	11/2/00
Amendment (BC)	5/8/01
Amendment (BC)	6/13/01
Amendment (AC)	7/3/01
Amendment (BC)	8/30/01
Amendment (BC)	11/20/01

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Bayer Corporation Pharmaceutical Division
Address:	400 Morgan Lane, West Haven, CT 06516
Representative:	Andrew Verderame, Associate Director, Regulatory Affairs
Telephone:	(203) 812-5172

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: AVELOX I.V.
b) Non-Proprietary Name (USAN): moxifloxacin hydrochloride in sodium chloride injection
c) Code Name/#: BAY 12-8039 (moxifloxacin hydrochloride)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: intravenous solution

12. STRENGTH/POTENCY: 0.16% (400 mg)

13. ROUTE OF ADMINISTRATION: intravenous

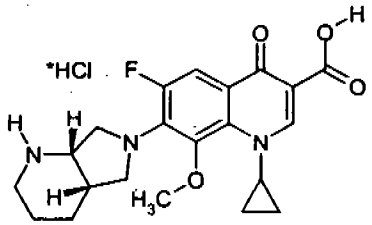
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Moxifloxacin Hydrochloride, $C_{21}H_{24}N_3FO_4$ x HCl, MW = 437.9
Monohydrochloride salt of 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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-085	AVELOX Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	10/22/01	N/A
OPDRA	Acceptable	4/26/01	Carol Holquist, R.Ph.
EA	Categorical exclusion	N/A	N/A
Microbiology	Acceptable	10/17/01	Vinnie Pawar, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL