

Reviewer's Comments

Almost half of the patients who took study drug complained of an adverse event. The incidence of adverse events was higher overall in the gatifloxacin treatment group. The most common adverse event experienced by patients on gatifloxacin was nausea, at twice the incidence rate.

It was also noted that there were more complaints of dizziness in the gatifloxacin treatment group, mostly seen in elderly females. These episodes were generally classified as mild, although there were two episodes classified as moderate and two episodes classified as severe in Study AI420-011. It was not possible to correlate whether there was any electrocardiographic abnormalities from the case report forms, as electrocardiograms were generally not performed when the patient was symptomatic.

8.6.3.2.2 Causally-Related

The types of adverse events that were assessed as being causally related by the investigator are summarized on the next page.

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Drug-related Adverse Events (All treated patients)

Adverse Clinical Event*	Gatifloxacin						Ciprofloxacin					
	011 N = 170		031 N = 189		Total N = 359		011 N = 180		031 N = 183		Total N = 363	
	N	%	N	%	N	%	N	%	N	%	N	%
Any AE	74	43.5	58	30.7	132	36.8	54	30	37	20.2	91	25.1
Nausea	27	15.9	21	11.1	48	13.4	13	7.2	10	5.5	23	6.3
Diarrhea	11	6.5	6	3.2	17	4.7	5	2.8	5	2.7	10	2.8
Dizziness	8	4.7	8	4.2	16	4.5	2	1.1	5	2.7	7	1.9
Headache	11	6.5	4	2.1	15	4.2	8	4.4	6	3.3	14	3.9
Vomiting	7	4.1	6	3.2	13	3.6	6	3.3	5	2.7	11	3
Vaginitis	8	4.7	3	1.6	11	3.1	3	1.7	1	0.5	4	1.1
Dry mouth	6	3.5	5	2.6	11	3.1	3	1.7	0	0	3	0.8
Pain Abdomen	5	2.9	4	2.1	9	2.5	3	1.7	3	1.6	6	1.7
Somnolence	4	2.4	4	2.1	8	2.2	1	0.6	1	0.5	2	0.6
Dyspepsia	3	1.8	4	2.1	7	1.9	5	2.8	3	1.6	8	2.2
Insomnia	5	2.9	1	0.5	6	1.7	1	0.6	2	1.1	3	0.8
Aesthenia	5	2.9	0	0	5	1.4	0	0	0	0	0	0
Constipation	2	1.2	2	1.1	4	1.1	4	2.2	0	0	4	1.1
Flatulence	0	0	3	1.6	3	0.8	0	0	1	0.5	1	0.3
Nervousness	2	1.2	0	0	2	0.6	2	1.1	0	0	2	0.6
Tremor	0	0	2	1.1	2	0.6	0	0	0	0	0	0
Vertigo	0	0	2	1.1	2	0.6	0	0	0	0	0	0

Reviewer's Comments

The majority of the adverse events attributed to study drug therapy revolved around the gastrointestinal system – nausea and diarrhea.

8.6.3.2.2.3 Serious Adverse Events

Out of 13 serious adverse events reported for Study AI420-011, none were assessed as being causally related to study drug therapy.

Study AI420-031 reported 25 serious adverse events. Five events (in two patients) were assessed as being potentially causally related to study drug therapy.

8.6.3.2.2.4 Severe or Life-Threatening Adverse Events

There were no severe or life-threatening adverse events reported for either study.

8.6.3.2.3 Discontinuation from Clinical Studies**8.6.3.2.3.1 Discontinuation from Clinical Studies due to Adverse Events**

Although the number of discontinuations from study drug were generally comparable between the treatment groups, there were more discontinuations from the gatifloxacin treatment group secondary to nausea and vomiting than from the ciprofloxacin treatment group.

8.6.3.2.3.2 Discontinuation from Clinical Studies due to Abnormal Laboratory Values

Although there were discontinuations because of abnormal laboratory values, these were secondary to an abnormal baseline value that was not recognized by the investigator until after a dose of study drug had already been administered.

Patients on gatifloxacin did develop abnormal laboratory values but these were generally mild. The few patients that did develop Grade III or IV abnormalities were nevertheless able to finish their course of therapy.

8.6.3.2.4 Hepatobiliary Abnormalities

There was no apparent correlation between liver enzyme abnormalities and gatifloxacin therapy in these clinical studies.

8.6.3.2.5 Pancreatic Enzyme Abnormalities

There did not appear to be any correlation between serum amylase elevations and gatifloxacin therapy in these clinical studies.

8.6.4 Special Populations

8.6.4.1 Gender, Age, and Ethnic Group

Efficacy

There were no differences observed in the efficacy rates between the treatment groups with respect to gender, age, or ethnic group.

Safety

In Study AI 420-031, there were no differences observed in the incidence of adverse events or laboratory abnormalities with respect to race or gender. More adverse events were observed in the older age groups for both treatment arms. This is not unexpected since older patients are more likely to have complicated medical histories and are more likely to be on multiple medications. Nevertheless, more events were observed in the gatifloxacin treatment arm than in the ciprofloxacin treatment arm. The significance of this finding is presently unknown.

In Study AI420-011, there were no differences observed in the incidence of adverse events or laboratory abnormalities with respect to race or age. There were a greater number of females with events in the gatifloxacin treatment group, but this was mirrored in the ciprofloxacin treatment group.

8.6.4.2 Pediatric Database

There were no pediatric patients enrolled in the clinical studies designed to support this indication. However, with the submission of the 4-month safety update (Amendment No. 12, Submission date 5 May 1999), the applicant indicated that they have begun clinical studies in the pediatric population. The first study is a pharmacokinetic assessment of an oral suspension in children under the age of 16 years.

8.6.5 Regulatory Recommendations

The medical officer recommendations for gatifloxacin regarding complicated the indications of urinary tract infection and pyelonephritis are:

1. Approval of gatifloxacin for the indication of treatment of complicated urinary tract infections (UTI) and pyelonephritis.
2. The label should indicate the pathogens for which the applicant was able to provide sufficient data to support their claims of efficacy.

8.6.6 Label Review

The portion of the label for this indication should be amended as follows:

Gatifloxacin is indicated for the treatment of "...complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*.

Pyelonephritis caused by *Escherichia coli*."

8.6.7 Phase IV Commitments

There are no Phase IV commitments for this indication.

/S/

Rigoberto Roca, M.D.
Reviewing Medical Officer

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Concurrences:

/S/

11/24/99

Joyce Korvick, M.D., M.P.H.
Lead Medical Officer
Division of Special Pathogen and
Immunologic Drug Products

/S/

11/24/99

Marc Cavaille-Coll, M.D., Ph. D.
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/S/

Mark Goldberger, M.D., M.P.H.
Division Director
Division of Special Pathogen and
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cc.

Original NDA 20-871

HFD-590/Div. Dir/Goldberger

HFD-590/Dep. Div. Dir/Albrecht

HFD-590/MedTL/Cavaillé-Coll

HFD-590/MO/Roca

HFD-590/Chem/Smith

HFD-590/Micro/Altaie

HFD-590/Pharmtox/Ellis

HFD-590/RPM/Atkins

HFD-590/RPM/Bernato

HFD-880/Biopharm/Uhl

HFD-725/Biometrics/Silliman

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Appendix A

Quinolones indicated for treatment of pyelonephritis:

1. Cipro® (ciprofloxacin)

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

2. Levaquin® (levofloxacin)

Complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*.

Acute pyelonephritis (mild to moderate) caused by *Escherichia coli*.

Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin. Therapy with levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

Quinolones indicated for treatment of infections of the urinary tract:

1. Cipro™ (ciprofloxacin)

As above.

2. Floxin™ (ofloxacin)

Complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter diversus**, or *Pseudomonas aeruginosa**

* = Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

3. Levaquin™ (levofloxacin)
As above.

4. Maxaquin™ (lomefloxacin)
Complicated Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Citrobacter diversus*,* or *Enterobacter cloacae*.*

NOTE: In clinical trials with patients experiencing complicated urinary tract infections (UTIs) due to *P. aeruginosa*, 12 of 16 patients had the microorganism eradicated from the urine after therapy with lomefloxacin. None of the patients had concomitant bacteremia. Serum levels of lomefloxacin do not reliably exceed the MIC of *Pseudomonas* isolates. THE SAFETY AND EFFICACY OF LOMEFLOXACIN IN TREATING PATIENTS WITH PSEUDOMONAS BACTEREMIA HAVE NOT BEEN ESTABLISHED.

*Although treatment of infections due to this microorganism in this organ system demonstrated a clinically acceptable overall outcome, efficacy was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before antimicrobial treatment in order to isolate and identify microorganisms causing infection and to determine their susceptibility to lomefloxacin. In patients with UTIs, therapy with Maxaquin film-coated tablets may be initiated before results of these tests are known; once these results become available, appropriate therapy should be continued. In patients with an acute bacterial exacerbation of chronic bronchitis, therapy should not be started empirically with lomefloxacin when there is a probability the causative pathogen is *S. pneumoniae*. Beta-lactamase production should have no effect on lomefloxacin activity.

5. Noroxin™ (norfloxacin)
Complicated urinary tract infections due to *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, or *Serratia marcescens**.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

6. Penetrex™ (enoxacin)
Complicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, or *Enterobacter cloacae**.

*Efficacy for this organism in this organ system at the recommended dose was studied in fewer than 10 infections.

Appendix B – List of Investigators (Study AI420-031)

Site #	Investigator	Affiliation	Location
003	Stephen Auerbach, M.D.	California Professional Research	Newport Beach, CA
004	Gary Brown, M.D.	PharmaTex Research	Amarillo, TX
005	Ronald Castellanos, M.D.	Clinical Physiology Associates	Fort Myers, FL
006	E. Wylly Killorin, M.D.	Shepherd Center, Inc.	Atlanta, GA
007	Frank Maggiacomo, D.O.	New England Center for Clinical Research	Cranston, RI
008	Michael McFadden, M.D.	Advanced Clinical Research	Salt Lake City, UT
009	Stuart Sarshik, M.D.	Stoneridge Professional Center	Sellersville, PA
010	Clair Cox, M.D.	University of Tennessee Urology Department	Memphis, TN
011	Howard Epstein, M.D.	University of Florida Health Science Ctr. Dept. Of Surgery Div. Of Urology	Jacksonville, FL
012	James Chris Jensen, M.D.	Clinical Research Advantage, Inc.	Salt Lake City, UT
014	Mary Ann Picone, M.D.	Bernard W. Gimbel MS Center	Teaneck, NJ
015	Walter Pitman, M.D.	Lloyd Noland Hospital Urology Ctr	Fairfield, AL
016	Barton Wachs, M.D.	Atlantic Urological Medical Group	Long Beach, CA
017	Ruben Garcia, M.D.	Private Office	Athens, TX
018	Courtenay Renneker, Jr., M.D.	Southern Drug Research, Inc.	Birmingham, AL
023	Roohollah Sharifi, M.D.	University of Illinois Dept. Of Urology Urology Clinic	Chicago, IL
024	Gholam Malek, M.D.	Jackson Foundation/Physicians Plus	Madison, WI
026	Sheldon Freedman, M.D.	Private Office	Las Vegas, NV
027	Robert Bettis, M.D.	Edmonds Family Medicine Clinic	Edmonds, WA
028	Louis Galdieri, M.D.	Physicians in Urology	Livingston, NJ
029	Donald Gleason, M.D.	Urological Associates of Southern Arizona	Tucson, AZ

Site #	Investigator	Affiliation	Location
030	Kevin Tomera, M.D.	Alaska Urological Assoc.	Anchorage, AK
031	William Moseley, M.D.	San Diego Uro-Research	San Diego, CA
032	W. Lamar Weems, M.D.	Mississippi Center of Clinical Research	Jackson, MS
034	Boris Kerzner, M.D.	Health Trends Research, LLC	Baltimore, MD
035	Thomas Marbury, M.D.	Orlando Clinical Research Center	Orlando, FL
036	Thomas Parkey, M.D.	Gabriel Clinical Research	Georgetown, TX
037	Eric Solomon, M.D.	Riverchase Clinical Research, PC	Birmingham, AL
041	Phillip McElvaine, M.D.	El Paso Emergency Physicians Group	El Paso, TX
042	H. Farris, M.D.	Woodward Medical Center	Greenville, SC
043	Lee Harbach, M.D.	San Diego Surgical Medical Group, Inc.	San Diego, CA
045	Warren Kessley, M.D.	San Diego Surgical Medical Group, Inc.	San Diego, CA
046	William King, M.D.	Urology Associates of New River Valley, PC	Radford, VA
047	George Fadda, M.D.	San Diego Surgical Medical Group, Inc.	San Diego, CA

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Appendix C – Adverse Clinical Events of All Causes, All Treated Patients (Study AI420-031)

Adverse Clinical Event ^a	Number (%) of Patients							
	Gatifloxacin (N = 189)				Ciprofloxacin (N = 183)			
	Related	Not Related	Not Assessed	Total	Related	Not Related	Not Assessed	Total
Any adverse event	58 (31)	34 (18)	4 (2)	97 (51)	38 (21)	37 (20)	4 (2)	79 (43)
Nausea	21 (11)	2 (1)	1 (<1)	24 (13)	11 (6)	0	0	11 (6)
Dizziness	8 (4)	4 (2)	2 (1)	14 (7)	5 (3)	0	0	5 (3)
Diarrhea	6 (3)	1 (<1)	0	7 (4)	5 (3)	4 (2)	0	9 (5)
Pain	0	5 (3)	2 (1)	8* (4)	0	1 (<1)	0	1 (<1)
Pain Back	1 (<1)	5 (3)	0	6 (3)	1 (<1)	3 (2)	0	4 (2)
Vomiting	6 (3)	0	0	6 (3)	5 (3)	0	0	5 (3)
Headache	4 (2)	2 (1)	0	6 (3)	6 (3)	4 (2)	0	10 (5)
Urinary Retention	0	5 (3)	0	5 (3)	1 (<1)	3 (2)	0	4 (2)
Dysuria	2 (1)	3 (2)	0	5 (3)	1 (<1)	10 (5)	1 (<1)	12 (7)
Pain Abdomen	4 (2)	1 (<1)	0	5 (3)	3 (2)	7 (4)	0	10 (5)
Dry Mouth	5 (3)	0	0	5 (3)	0	0	0	0
Constipation	2 (1)	1 (<1)	1 (<1)	4 (2)	0	0	1 (<1)	1 (<1)
Dyspepsia	4 (2)	0	0	4 (2)	3 (2)	0	1 (<1)	4 (2)
Hematuria	2 (1)	2 (1)	0	4 (2)	0	5 (3)	0	5 (3)
Somnolence	4 (2)	0	0	4 (2)	1 (<1)	0	0	1 (<1)
Flatulence	3 (2)	0	0	3 (2)	1 (<1)	1 (<1)	0	2 (1)

Indication: Complicated Urinary Tract Infections

Number (%) of Patients

Adverse Clinical Event ^a	Gatifloxacin (N = 189)				Ciprofloxacin (N = 183)			
	Related	Not Related	Not Assessed	Total	Related	Not Related	Not Assessed	Total
Pharyngitis	1 (<1)	4 (2)	0	5 (3)	0	5 (3)	0	5 (3)
Dysmenorrhea	0	3 (2)	0	3 (2)	0	0	0	0
Nocturia	0	2 (1)	0	3 *(2)	0	1 (<1)	0	1 (<1)
Urinary Incontinence	0	3 (2)	0	3 (2)	0	6 (3)	1 (<1)	7 (4)
Vaginitis (% women)	3 (2)	0	0	3 (2)	1 (<1)	2 (1)	0	3 (2)
Accidental Injury	0	1 (<1)	0	1 (<1)	1 (<1)	2 (1)	0	3 (2)
Asthenia	1 (<1)	1 (<1)	0	2 (1)	1 (<1)	2 (1)	0	3 (2)
Fever	0	1 (<1)	0	1 (<1)	0	4 (2)	0	4 (2)
Rash	1 (<1)	1 (<1)	0	2 (1)	1 (<1)	2 (1)	0	3 (2)
Urinary Frequency	0	2 (1)	0	2 (1)	0	4 (2)	0	4 (2)
Urinary Urgency	1 (<1)	1 (<1)	0	2 (1)	0	4 (2)	1 (<1)	5 (3)

^a A patient may have more than one adverse event. Only those adverse events occurring in 2% or more of the patients in either treatment group are listed.

* For one patient, the relationship of the adverse event to study drug was not recorded.

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Appendix D - List of Investigators (Study AI420-011)

Site #	Investigator	Affiliation	Location
004	Ira Klimberg, M.D.	The Urology Center of Florida, Inc.	Ocala, FL
005	Marc Gittleman, M.D.	South Florida Medical Research	Aventura, FL
006	Jay Young, M.D.	South Coast Urological Medical Research Group	Laguna Hills, CA
007	W. Glen Wells, M.D.	Alabama Urology Associated P.C.	Birmingham, AL
008	Eugene Dula, M.D.	West Coast Clinical Research	Van Nuys, CA
009	Jacques Susset, M.D.	MultiMed Research	Providence, RI
010	David Winchester, M.D.	The Urology Clinic, P.C.	Portland, OR
011	Daniel Saltzstein, M.D.	Urology San Antonio, PA	San Antonio, TX
012	Peter Knapp, M.D.	Urology of Indiana, L.L.C.	Indianapolis, IN
013	James McMurray, M.D.	Medical Affiliated Research Center	Huntsville, AL
014	Robert Feldman, M.D.	Urology Specialists P.C.	Waterbury, CT
015	Joel Kaufman, M.D.	UroFitness	Aurora, CO
016	Harin Padma-Nathan, M.D.	The Male Clinic	Santa Monica, CA
017	Mark Ratner, M.D.	Urological Consultants, P.A.	Rockville, MD
018	Stacy Childs, M.D.	Cheyenne Urological, P.C.	Cheyenne, WY
019	Christopher Steidle, M.D.	Northeast Indiana Urology, P.C.	Fort Wayne, IN
020	John Tuttle, M.D.	Network Trials, Inc.	Lexington, KY
021	Norman Zinner, M.D.	Western Clinical Research, Incl.	Torrance, CA
022	C. Gilberto Brito, M.D.	Urology Associates, Ltd.	Phoenix, AZ
023	Jeffrey Snyder, M.D.	Genitourinary Surgical Consultants, P.D.	Denver, CO
024	Doria Grimard, M.D.	Complexe Hospitalier De La Sagamie	Chicoutimi, Quebec, Canada
026	John Grantmyre, M.D.	QEII Health Science Center, New Halifax Infirmary Site, Urology Clinic Level	Halifax, Nova Scotia, Canada
028	Lindsay Nicolle, M.D.	Health Science Center Department of Medicine	Winnipeg, Canada
029	Thomas J. Louie, M.D.	Bow Valley General Hospital	Calgary, Alberta, Canada
030	Claude St. Pierre, M.D.	Novabyss Inc.	Sherbrooke, Quebec, Canada

Appendix E - Adverse Clinical Events of All Causes, All Treated Patients (Study AI420-011)

Adverse Clinical Event ^a	Number of Patients (%)							
	Gatifloxacin N = 170				Ciprofloxacin N = 180			
	Related	Not Related	Not Assessed	Total	Related	Not Related	Not Assessed	Total
Any adverse event	74 (44)	38 (22)	1 (<1)	113 (67)	54 (30)	46 (26)	2 (1)	102 (57)
Nausea	27 (16)	3 (2)	0	30 (18)	13 (7)	3 (2)	0	16 (9)
Headache	11 (6)	5 (3)	0	16 (9)	8 (4)	7 (4)	0	15 (8)
Dizziness	8 (5)	6 (4)	0	14 (8)	2 (1)	1 (<1)	0	3 (2)
Diarrhea	11 (6)	0	0	11 (6)	5 (3)	2 (1)	0	7 (4)
Pharyngitis	1 (<1)	9 (5)	1 (<1)	11 (6)	0	3 (3)	0	3 (3)
Pain Abdomen	5 (3)	4 (2)	0	9 (5)	3 (2)	4 (2)	0	7 (4)
Vaginitis (% women)	8 (10)	1 (1)	0	9 (11)	3 (3)	1 (<1)	0	4 (4)
Hematuria	0	8 (5)	1 (<1)	9 (5)	0	3 (2)	0	3 (2)
Pain Back	1 (<1)	5 (3)	2 (1)	8 (5)	3 (2)	6 (3)	0	9 (5)
Vomiting	7 (4)	1 (<1)	0	8 (5)	6 (3)	2 (1)	0	8 (4)
Dysuria	1 (<1)	5 (3)	1 (<1)	7 (4)	0	4 (2)	0	4 (2)
Dry Mouth	6 (4)	0	0	6 (4)	3 (2)	2 (1)	0	5 (3)
Asthenia	5 (3)	1 (<1)	0	6 (4)	0	0	1 (<1)	1 (<1)
Dyspepsia	3 (2)	2 (1)	0	5 (3)	5 (3)	0	0	5 (3)
Somnolence	4 (2)	1 (<1)	0	5 (3)	1 (<1)	1 (<1)	0	2 (1)

Indication: Complicated Urinary Tract Infections

Adverse Clinical Event ^a	Number of Patients (%)							
	Gatifloxacin N = 170				Ciprofloxacin N = 180			
	Related	Not Related	Not Assessed	Total	Related	Not Related	Not Assessed	Total
Insomnia	5 (3)	0	0	5 (3)	1 (<1)	1 (<1)	0	2 (1)
Urinary Frequency	0	5 (3)	0	5 (3)	0	8 (4)	0	8 (4)
Chills	1 (1)	3 (2)	0	4 (2)	0	1 (<1)	0	1 (<1)
Urinary Urgency	0	4 (2)	0	4 (2)	0	3 (2)	0	3 (2)
Rhinitis	0	4 (2)	0	4 (2)	0	2 (1)	0	2 (1)
Constipation	2 (1)	1 (<1)	0	3 (2)	4 (2)	2 (1)	1 (<1)	7 (4)
Rash	0	3 (2)	0	3 (2)	4 (2)	1 (<1)	0	5 (3)
Fever	1 (<1)	2 (1)	0	3 (2)	0	3 (2)	0	3 (2)
Nocturia	0	2 (1)	1 (<1)	3 (2)	0	4 (2)	0	4 (2)
Urinary Retention	0	3 (2)	0	3 (2)	0	4 (2)	0	4 (2)
Pain	1 (<1)	2 (1)	0	3 (2)	0	6 (3)	0	5 (3)
Urinary Incontinence	0	3 (2)	0	3 (2)	0	3 (2)	0	3 (2)
Herpes Simplex	0	3 (2)	0	3 (2)	0	1 (<1)	0	1 (<1)
Spasm	2 (1)	1 (1)	0	3 (2)	0	4 (2)	0	4 (2)
Edema Peripheral	1 (<1)	0	1 (<1)	2 (1)	1 (<1)	2 (1)	0	3 (2)
Coughing	0	2	0	2 (1)	1 (<1)	3 (2)	0	4 (2)
Nervousness	2 (1)	0	0	2 (1)	2 (1)	1 (<1)	0	3 (2)
Pain Bone	0	1 (<1)	0	1 (<1)	1 (<1)	2 (1)	0	3 (2)

Indication: Complicated Urinary Tract Infections

Adverse Clinical Event ^a	Number of Patients (%)							
	Gatifloxacin N = 170				Ciprofloxacin N = 180			
	Related	Not Related	Not Assessed	Total	Related	Not Related	Not Assessed	Total
Sweating	1 (<1)	0	0	1 (<1)	2 (1)	1 (<1)	0	3 (2)
Sinusitis	0	0	0	0	1 (<1)	2 (1)	0	3 (2)
Allergic Reaction	0	0	0	0	1 (1)	2 (1)	0	3 (2)

^a All adverse clinical events occurring in 2% or more of the patients in either treatment group are listed.

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Indication: Complicated Urinary Tract Infections

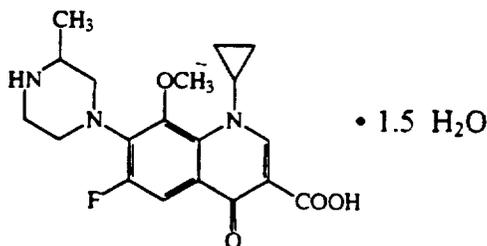
8.7 Medical Officer Review of NDA 21-061: Gatifloxacin (Tequin™) for the treatment of Uncomplicated Gonorrhea

Date Submitted: 28 December 1998
Date Received: 29 December 1998
Date Assigned: 29 December 1998
Date Completed: 9 September 1999

Applicant: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, Connecticut 06492
203-677-6883

Contact person: Douglas Kriesel, Ph.D.

Drug: Proprietary name - Tequin™
Generic name - Gatifloxacin
Chemical name - (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate
Molecular formula - C₁₉H₂₂FN₃O₄ • 1.5 H₂O
Molecular weight - 402.42 (sesquihydrate)
Molecular structure -



Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400-mg tablets (21-061)

Related NDA: 21-061, 21-062

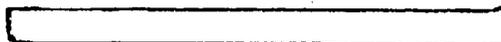


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ON ORIGINAL**

8.7.1 INTRODUCTION:

The original NDA's for Tequin (gatifloxacin) Tablets, NDA 21-061 and for Tequin IV, NDA 21-062, were submitted December 28, 1998 and the applicant requested approval for seven different indications:

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

The review of these indications has been divided among several reviewers. This document summarizes the results of the medical review of the indication for UNCOMPLICATED GONORRHEA in males and females.

COMMENT:

In addition to completing the review of the indication, a second goal of this process was to learn and use the electronic version of the NDA submission to perform this review.

The applicant originally came to the agency with the proposal to use a customized program called "I Review" for the analysis of the data. This program was based on previous computer submissions to the agency and provided the reviewer with the ability to analyze efficacy and demographic data, and generate summary tables of outcome based on all patients or selected subsets of patients. The program as presented did not include a presentation and analysis of safety data, although the applicant did offer to expand I Review to include safety data and any other information deemed necessary.

In view of the Center's existing Guidance on Electronic Submissions (www.fda.gov/cder/guidances/index.htm), the company was asked to submit data files in SAS-transport format which could be used with the JMP program recommended by the Center. The applicant submitted data in files as requested, along with case report forms and patient profiles for all patients enrolled in the trial (728 patients) in PDF format and Word documents for the study report for the trial.

The electronic case report forms included the following data: demographic information, inclusion criteria, exclusion criteria, medical history checklist, previous antimicrobial use, concurrent infection disease diagnoses, culture and susceptibility results, adverse events, outcome. In addition, comprehensive monitor correction sheets were included.

occasionally with 3 to 5 copies of the same page scanned among the CRF pages. Notably absent from the scanned case report forms were laboratory results sheets. Thus, no independent verification of laboratory test findings could be performed; however, the verification and analysis of all laboratory data and safety of the drug has been undertaken by Dr. Korvick.

The datasets were complete; the data was provided in many forms and files. Data fields were referenced in the annotated case report forms, the names were generally a string of letters (acronym-style) for the field. Some information was presented as text and not numeric entries (so could not calculate number of days between treatment and follow up, for example).

While the agency requested that the applicant submit the data in SAS-transport and JMP in compliance with the Agency Guidance to Industry document, the difficulty in using JMP is that analyses required numerous repetitive steps and tasks with no ready way for the program to track the steps. So from the demographic files, for example, it was not possible to promptly generate a tabulation of all patients, treated patients and evaluable patients based on relevant factors such as gender, race, age. This information could be generated in a stepwise fashion for variables of interest. Culture result information, which constitutes the primary efficacy variable, was provided in a easy to sort, friendly format where the entry cultures could be compared to the follow up cultures, and where the sites of infection could be analyzed separately without having to go through multiple steps of subsetting. Unfortunately, this program did not have a feature where tables of summary results could be readily imported into a wordprocessing document. Thus, a fair amount of time was spent transferring information from JMP to wordprocessing.

PROPOSED INDICATION:

The applicant is requesting approval of the following wording for the gonorrhea indication:

Uncomplicated urethral, pharyngeal and rectal gonorrhea in males and endocervical, pharyngeal, and rectal gonorrhea in females caused by to *Neisseria gonorrhoeae*. (See WARNINGS.)

Within the WARNINGS section, there is the class labeling statement,

Gatifloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

Under **DOSAGE AND ADMINISTRATION**, the proposed regimen for the treatment of gonorrhea is 400 mg of gatifloxacin, given as a single oral dose.

STUDIES SUBMITTED:

In support of the proposed labeling statements, the applicant has submitted results of one clinical trial. Study No. AJ420-012:

This was a randomized, double-blind, multicenter, phase III study of two single dose regimens of gatifloxacin (400 mg and 600 mg) and a single dose of ofloxacin (400 mg) in the treatment of uncomplicated gonococcal infection. The trial was conducted at 13 centers in the US between August 1997 and May 1998. A total of 738 patients were enrolled in a 2:2:1 randomization scheme; 295 received gatifloxacin 400 mg; 291 received gatifloxacin 600 mg and 142 received ofloxacin 400 mg (10 patients did not receive any drug).

A second stated objective of the trial was to assess the activity of a single dose of gatifloxacin against *Chlamydia trachomatis* cervicitis (females) and urethritis (males).

The applicant reports a bacterial efficacy of greater than 95% in the eradication of *Neisseria gonorrhoeae* from urethral and cervical sites, as well as rectal and pharyngeal sites.

REGULATORY CONSIDERATIONS:

In 1992, the Division of Anti-Infective Drug Products (DAIDP) made available the POINTS TO CONSIDER document and in 1998, the draft Guidance to Industry document on *Uncomplicated Gonorrhea -- Developing Antimicrobial Drugs for Treatment* was made available. Both of these documents address the topic of uncomplicated gonorrhea.

For approval of the indication of uncomplicated gonorrhea, it is expected that at least 100 male and at least 100 female patients be evaluable for bacterial eradication and that at least 95% of these patients have *Neisseria gonorrhoeae* eradicated from the urethral and cervical site, respectively. For the approval of rectal and pharyngeal infections, it is recommended that data from at least 20 patients per gender per site (per drug) be evaluated and that at least 90% of the isolates for each of these subgroups be eradicated.

It is recommended that results of clinical trials of uncomplicated gonorrhea focus on bacterial eradication of *Neisseria gonorrhoeae* as the primary endpoint, and that eradication be assessed from a repeat culture taken 3-7 days after the single-dose treatment, this time frame should be extended for a drug with a longer half-life.

COMMENT:

A brief examination of the studies submitted in preparation for the 45-day filing meeting indicated that these issues were taken into consideration by the company. However, it is possible that not all sites in each gender will be approvable. This is addressed in greater detail in this review.

8.7.2 REVIEW OF STUDY AI420-012: A randomized, double-blind, multicenter, phase III study of two single dose regimens of gatifloxacin and a single dose of ofloxacin in the treatment of uncomplicated gonococcal infections.**8.7.2.1 STUDY DESIGN:**

The study was a double-blind, double-dummy trial conducted at 13 centers in the USA, comparing 2 doses of gatifloxacin to ofloxacin in a 2:2:1 randomization for the treatment of gonorrhea. The plan was to enroll up to 812 patients ages 16 and over. Enrollment was increased from 625 by Amendment 1, in order to (1) achieve a total of 100 evaluable males with urethral infection and a total of 100 evaluable female with cervical infection treated with each gatifloxacin dose and (2) demonstrate equivalence of at least one gatifloxacin dose to ofloxacin.

COMMENT:

The regulatory recommendation for approval of an antimicrobial in the treatment of uncomplicated gonorrhea is a minimum bacterial eradication rate of 95%, as stated above. There is not further need to demonstrate statistical equivalence to an approved agent per se, although a comparison of the bacterial, clinical and safety outcome to an approved regimen provides useful information on the drug.

PURPOSE:

- To demonstrate the safety and effectiveness of two doses of gatifloxacin (400mg, 600 mg) orally, compared to ofloxacin 400 mg orally, in the treatment of uncomplicated gonorrhea in male and female patients.
- To assess the activity of gatifloxacin as single dose therapy for uncomplicated *Chlamydia trachomatis* urethritis in men and cervicitis in women. (Site 5- Hook and Site 9- Jones)

STUDY CONDUCT: August 1, 1997 to May 1, 1998

INCLUSION CRITERIA:

all of the following criteria had to be met:

- outpatient men or women ≥ 16 years of age were enrolled and treated with either

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- gatifloxacin tablets or ofloxacin capsules, packaged in blister packs
- written informed consent was obtained (enrollment and consent age were in compliance with local laws and regulations)
- women of childbearing potential had to have a negative urine or serum pregnancy test within 48 hours prior to study entry and agree to use effective birth control method during the study
- females
 - history of positive test for gonorrhea untreated within 14 days of enrollment
 - Gram stain or gentian violet stain showing PMLs with intracellular Gram-negative diplococci with or without a history of sexual exposure within 14 days to a man with culture-documented urethral gonorrhea.
 - history of sexual exposure within 14 days to a man with culture-documented urethral gonorrhea and/or who had Gram stain or gentian violet stain showing PMLs with intracellular Gram-negative diplococci
- males
 - Gram stain or gentian violet stain showing PMLs with intracellular Gram-negative diplococci

EXCLUSION CRITERIA:

- signs or symptoms of complicated gonorrhea (e.g. endocarditis, arthritis, PID, ophthalmitis)
- confirmed or suspected syphilis
- pregnant or nursing women
- treatment with systemic antibiotic within 72 hours prior to entry into study
- history of hypersensitivity reaction to fluoroquinolones
- evidence of significant gastrointestinal disorder or malabsorption that may inhibit absorption
- known renal insufficiency (serum creatinine \geq 1.5 mg/dL or requiring renal dialysis)
- hepatic disease (ALT and/or AST and/or \geq 3 times ULN)
- patient likely to be noncompliant with the protocol

Patients with a suspected concurrent infection with *Chlamydia trachomatis* could be enrolled at the discretion of the investigator. It was recommended that these patients were given appropriate *Chlamydia* therapy at the day +4 to +10 visit.

DRUGS AND DOSAGE REGIMEN:

Gatifloxacin 400 mg or 600 mg orally, single-dose administered as two tablets (or matching placebo)

Ofloxacin 400 mg orally, single-dose administered as two capsules (or matching placebo).

Ofloxacin at this dose is approved for the treatment of uncomplicated cervical and/or urethral gonorrhea.

BLINDING: Study medication was administered in a double-dummy double blind fashion. Study medication (active drug and matching placebo) were prepared in film-coated tablets (400 mg gatifloxacin, 600 mg gatifloxacin, matching placebo) or as gray opaque capsules (400 mg ofloxacin, matching placebo) to obscure their identifies; these were supplied in blinded blister cards. Each patient received two tablets and two capsules.

All drug doses were administered in the clinic under direct observation. Dosing was to be done two hours before or two hours after a meal or after use of antacid.

The randomization system used a dynamic balancing algorithm to minimize imbalance of treatment arms within gender, site (see statistical review for discussion of this methodology)

CONCOMITANT MEDICATIONS:

No concomitant systemic antibiotic was allowed, unless the patient was a treatment failure. After completion of the final evaluation visit, patients were treated with either doxycycline or other agent for culture-positive *Chlamydia trachomatis*.

PRETREATMENT PROCEDURES:

Within 48 hours of study entry, patients had a history and physical exam, assessment of vital signs, signs and symptoms of infection, labs (hematology, chemistry, urinalysis), RPR/VDRL and urine pregnancy test (females).

Cultures for *N. gonorrhoeae* were taken from urethra, pharynx and rectum (optional) in males and from the cervix, rectum, pharynx and urethra (if the patient was status post hysterectomy and did not have a cervix) in females.

Susceptibility testing was to be performed by disk diffusion and agar dilution for all *N. gonorrhoeae* isolates, the tentative interpretive criteria were as follows: Susceptible ≤ 0.125 mcg/mL (≥ 38 mm), Intermediate 0.25 mcg/mL (34-37 mm), Resistant > 0.5 mcg/mL (≤ 35 mm)

Investigators kept a screening log of all patients presumed to have a diagnosis of gonorrhea and stated a reason for any patients who were not subsequently randomized into the study.

POSTTREATMENT PROCEDURES:

Patients were seen +4 to +10 days after receiving treatment. The pretreatment procedures were repeated, in addition patients were questioned about compliance with protocol instructions and adverse events.

EFFICACY EVALUATION:**Bacteriological Outcome:**

The primary endpoint of the trial was bacteriological response by infection site as assessed at day +4 to +10 post treatment in evaluable patients (test of cure visit).

COMMENT:

As noted above, the Guidance document recommends a follow-up culture at 3 - 7 days after treatment of uncomplicated gonorrhoea. However, because gatifloxacin has a half-life of 7 hours (appx), it is justified to use a longer follow-up period for evaluation. Therefore, the timing selected in the protocol amendment is appropriate and acceptable.

Bacteriological response to therapy was to be assessed based on a comparison of the bacterial culture pre-therapy and at the post treatment visit.

COMMENT: Bacterial response, by site of infection, is considered the primary efficacy endpoint. Thus, all patient profiles / case report tabulations (CRTs) were examined for consistency with the protocol. In addition, a random sample of case report forms (CRFs) was evaluated to determine consistency in data transfer from the CRF to the CRTs, and to evaluate interpretation of patient data. The majority of this examination consisted of verifying the bacteriological data, although some demographic, dosing, concomitant medication and conditions, clinical course and adverse events were also checked. As stated below, there was agreement with the information presented. Such consistency between the applicant's and reviewer's analysis may be a reflection of the clear direction and information contained in the Guidance to Industry document on Uncomplicated Gonorrhoea, the investigators compliance with the protocol, a rigorous monitoring program, and the applicant's attention to complete data collection of the key variables.

Bacteriological outcome, by site, was classified as follows:

Eradication: *N. gonorrhoeae* not present in the post-treatment culture at 4-10 days.

Persistence: Isolation of *N. gonorrhoeae* from the post-treatment culture at 4-10 days.

In addition eradication or persistence of *C. trachomatis* was assessed at sites 05 and 09.

Clinical Outcome:

Clinical response to therapy was to be assessed by the sponsor on day +4 to +10 and based on the

investigator's assessment of the patient's clinical condition before and after treatment.

COMMENT:

Review of selected case report forms and patient profiles, and assessment of clinical outcome showed that the definition of clinical outcome was correctly applied in classifying patient outcome.

Clinical outcome was classified by the applicant as the following:

Symptoms Resolved/Cure: complete resolution of signs and symptoms

Symptomatic: no apparent response to therapy, continuation of signs and symptoms

Unable to determine: no assessment of signs and symptoms

SAFETY EVALUATION:

Adverse events and laboratory tests were monitored between the day of dosing and 30 days post-treatment (Day +30). In the case of this indication, the final assessment was made during the day 4-10 post treatment visit.

COMMENT:

Because this drug is also being evaluated for multiple other indications at multiple dose regimens ranging from 200 mg for 3 days in UTI to 400 mg up to 14 days for other indications, a full assessment of gatifloxacin's safety profile is deferred to the primary reviewer. A summary of adverse events and laboratory changes from the gonorrhea study is provided in this review.

8.7.2.2 EVALUATION OF EFFICACY:

RESULTS OF STUDY 420-012:

A total of 738 male and female patients were enrolled at 13 centers in the United States. Ten patients did not receive drug.

There were 295 patients (137 men, 158 women) randomized to 400 mg gatifloxacin, 291 patients (137 men, 154 women) randomized to 600 mg gatifloxacin and 142 patients (66 men, 76 women) randomized to ofloxacin.

Among the enrolled patients, 554 were considered evaluable. This included 218 patients (117 men, 101 women) in the 400 mg gatifloxacin arm, 226 (122 men, 104 women) in the 600 mg gatifloxacin arm and 110 (55 men, 55 women) in the ofloxacin arm.

Enrollment by center and the number of patients considered evaluable by the applicant is presented in Table 1 below:

Table 1. PATIENT ENROLLEMENT

Center	Investigator	Enrolled	Treated	Evaluable
001	David H. Martin, M.D. New Orleans, LA	101	101	77
006	Bradley Stoner, M.D., Ph.D. St. Louis, Missouri	101	101	73
005	Edward W Hook, III, M.D. Birmingham, Alabama	98	98	77
004	John M Douglas, Jr. M.D. Denver, Colorado	94	91	80
009	Robert Jones, M.D. Indianapolis, Indiana	81	80	51
007	Peter Leone, M.D. Raleigh, N.C.	69	68	50
002	William M McCormack, M.D. Brooklyn, NY	65	65	54
010	Tomasz Mroczkowski M.D. New Orleans, Louisiana	60	60	53
015	Ziad A. Dalu, M.D. St. Louis, Missouri	25	22	14
003	H. Hunter Handsfield, M.D. Seattle, Washington	22	22	13
016	Peter Alan Rice, M.D. Boston, Massachusetts	10	10	7
011	Romina Kee, M.D. Chicago, Illinois	10	8	0
019	Linda Duffy, M.D. Buffalo, New York	2	2	0
TOTALS		738	728	554

COMMENT:

The reviewer concurs in general with the data on enrollment and evaluability. In addition to the patients considered evaluable by the applicant, the reviewer added a few female patients as evaluable for pharyngeal and rectal sites of infection (next page).

Table 2. REASONS FOR EXCLUSION OF PATIENTS

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Enrolled	296	296	146
Males	138	139	68
Females	158	157	78
Reason for Excluding Patient			
Negative or No culture	55	48	22
No follow up visit	19	15	10
Did not receive drug	1	5	4
other (can't find)	3	2	0
Evaluable patients	218	226	110
Males	117	122	55
Females	101	104	55

COMMENT:

Two patients in the 400 mg arm (01-341, 10-377), one patient in the 600 mg arm (07-666) and one patient in the ofloxacin arm (1-508) did not have a primary genital site of infection and had only pharyngeal or rectal involvement. These patients had been considered clinically nonevaluable by the applicant. Their microbiological data is considered valid and they are included in the bacteriological outcome evaluable group, changing slightly the number of eradicated pharyngeal and rectal isolates but not resulting in a different regulatory recommendation.

DEMOGRAPHIC CHARACTERISTICS for the treated population and the clinically evaluable population are presented in Tables 3 and 4, respectively.

Table 3. DEMOGRAPHIC CHARACTERISTICS OF ALL TREATED PATIENTS

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
N=	295	291	142
Gender			
Males	137	137	66
Females	158	154	76
Race			
White	19	22	4
Black	267 (91%)	261 (90%)	131 (92%)
Others	9	8	7
Age (years)			
Mean	25	26	27
Range	16-55	16-54	17-55
Weight (kg)			
Mean	73	74	73
Range	41-141	43-160	45-127

Table 4. DEMOGRAPHIC CHARACTERISTICS OF ALL EVALUABLE PATIENTS

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
N=	218	226	110
Gender			
Males	117	122	55
Females	101	104	55
Race			
Black	218	226	110
Age (years)			
Mean	26	26	26
Range	16-55	16-54	17-47
Weight (kg)			
Mean	74	75	74
Range	41-141	43-160	45-127

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COMMENT:

There are no significant differences between the demographic characteristics of the treated population and the evaluable population.

PAST MEDICAL HISTORY:

In each of the treatment arms, approximately half the patients gave a history of a previous sexually transmitted disease (STD), including about one-third of the males and 20% of the females reported a history of gonorrhea, a third reported tobacco use, 20% reported alcohol use or drug use, and 11% reported allergies/drug sensitivity. Concurrent *Chlamydia* was documented in approximately 9% of male patients and 20% of female patients. In addition, approximately 13% of women had bacterial vaginosis, 9% had yeast infection and 8% had *Trichomonas* concurrently. Four patients with HIV were enrolled in the study. Again, these conditions were reasonably balanced across the treatment groups.

8.7.2.2.1 BACTERIOLOGICAL OUTCOME IN BACTERIOLOGICALLY EVALUABLE PATIENTS**Table 5. BACTERIOLOGICAL ERADICATION RATES IN MALES:**

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Urethra	116/117 (99%)	122/122 (100%)	55/55 (100%)
Pharynx	3/3	5/5	1/1
Rectum	0	0	0

COMMENT:

Among male patients, essentially all patients had cultures of the urethra and pharynx in all three arms; however, rectal cultures were only done in 11 gatifloxacin and no ofloxacin patient. Therefore, the conclusion that can be pharyngeal cultures were positive in a very small fraction of patients, and there are no rectal isolates because so few patients were cultured (presumably because of lack of exposure history).

The one patient who had persistence of gonorrhea after treatment with 400 mg gatifloxacin reported reexposure to an infected partner on day 4. While this may therefore represent a reinfection, in the worst case scenario it is included as a persistence.

The bacteriological results presented above indicate that gatifloxacin at either 400 mg or

600 mg PO is 99% effective in eradicating gonorrhea from the urethra in men. However, the data to make any conclusions about rectal or pharyngeal gonorrhea are inadequate.

Table 6. BACTERIOLOGICAL ERADICATION RATES IN FEMALES:

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Cervix	100/101 (99%)	103/104 (100%)	55/55 (100%)
Rectum	21/21 (100%)	16/16	8/8
Pharynx	7/7	15/15	3/3

COMMENT:

Examination of the culture data listings showed that essentially all female patients in all three arms had endocervical, pharyngeal and rectal cultures done, and only two females had urethral cultures instead of endocervical. Among those screened, approximately 20% had positive rectal cultures and a smaller proportion had positive pharyngeal cultures.

The bacteriological results presented above indicate that gatifloxacin is 99% effective at each dose in eradicating gonorrhea from the cervix in women.

In addition, the data are adequate to support approval of treatment of rectal gonorrhea in women.

The information on pharyngeal gonorrhea treatment is marginal. Even after including the additional two female patients to each of the two gatifloxacin arms, the number of eradicated cases is 7/7 for 400 mg and 15/15 for 600 mg -- this information is adequate to support recommending 600 mg of gatifloxacin in the treatment of pharyngeal gonorrhea (because one can use the 400 mg data to support the efficacy of the 600 mg dose; not visa versa), but does not support approval of the 400 mg dose.

While either the 400 mg or the 600 mg gatifloxacin regimen is effective in the treatment of cervical and rectal gonorrhea in women, only 600 mg gatifloxacin has been shown to be effective in pharyngeal gonorrhea in women. It is possible that 400 mg may be effective, but there are inadequate data to support this hypothesis.

Susceptibility Testing

The majority of isolates were tested for susceptibility to quinolones (gatifloxacin, ciprofloxacin, ofloxacin) and for beta-lactamase production. More than 99% of the isolates had an MIC to

gatifloxacin of 0.016 mcg/mL or less. Two isolates from female patients showed reduced susceptibility with MICs of 0.125 mcg/mL and 0.25 mcg/mL. The latter isolate was also frankly resistant to ofloxacin with an MIC of 2 mcg/mL.

Beta-lactamase production was identified in approximately 10% of all *Neisseria gonorrhoeae* isolated from male patients and in approximately 5% of all isolates from female patients. However, because the mechanism of action of the quinolones is different from beta-lactams and there is to date no evidence of cross-resistance / multiple drug resistance between these drug classes, therefore this information is not reflected in the package insert for this indication.

Table 7. Beta-lactamase positive isolates identified among *N. gonorrhoeae* isolates tested

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Males	12/126 (10%)	12/125 (10%)	4/59 (7%)
Females	5/103 (5%)	5/107 (5%)	2/54 (4%)

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8.7.2.2.2 CLINICAL OUTCOME was reported by the applicant and is presented below:

Table 8. CLINICAL OUTCOME IN MALES:

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Symptoms resolved	112/117 (96%)	113/118 (96%)	53/55 (100%)
Symptoms persisted	5/117	5/118	2/55
Asymptomatic on entry	0	4	0

Table 9. CLINICAL OUTCOME IN FEMALES:

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Symptoms resolved	57/79 (72%)	62/86 (72%)	36/46 (78%)
Symptoms persisted	21/79	24/86	10/46
Asymptomatic on entry	22	18	9

COMMENT:

As seen above, more women than men were asymptomatic. This finding is consistent with the epidemiology of gonorrhea. In addition, despite high eradication rates of gonorrhea in all three arms, there is persistence of clinical symptoms of vaginal infection in approximately one-fourth of the females. This may be accounted for partly by the presence of other STDs in some of the patients at entry, but also due to the reports of vaginitis developing in patients after treatment. The incidence of vaginitis due to candida, as verified by the reviewer, was higher in the gatifloxacin arms: 12% in 400 mg, 9% in 600mg and 6% in the ofloxacin arm, respectively.

STATISTICAL EVALUATION:

The applicant performed a 95% C.I. test for the study and the evaluable population actually fell within their planned + or - 10%. However, calculation of a 95% C.I. is not necessary in this indication, where the lowest acceptable limit of the point estimate is 95% for women as well as for men, based on a minimum of 100 culture-positive patients per gender.

8.7.2.3 EVALUATION OF SAFETY:**SAFETY RESULTS:****8.7.2.3.2 ADVERSE EVENTS OF ALL CAUSES/ RELATIONSHIP**

In this study, only single doses of gatifloxacin 400 mg or 600 mg were tested. In the other indications, multiple dose regimens up to 400 mg for 14 days were tested. Thus, the information below represents the findings from this single dose study and may not reflect findings seen in multiple dose studies.

No patient discontinued the study drug because only a single dose was administered. The most commonly reported adverse events were nausea, vaginitis and headache and most events were considered mild in severity.

(The following 2 tables were presented as table 12.1.1 page 00096 and 12.1.2 page 00098 in the applicant's submission).

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Table 10 Adverse Clinical Events of All Causes, by Relationship to Study Drug, All Treated Patients Protocol A1420-012

Adverse Event ^a	Number (%) of Patients											
	Gatifloxacin 400 mg (N = 295)				Gatifloxacin 600 mg (N = 291)				Ofloxacin 400 mg (N = 142)			
	Related	Not Related	Unassessed	Total	Related	Not Related	Unassessed	Total	Related	Not Related	Unassessed	Total
<u>Any Adverse Clinical Event</u>	65 (22)	16 (5)	2 (<1)	83 (28)	76 (26)	22 (8)	3 (1)	101 (35)	26 (18)	14 (10)	2 (1)	42 (30)
Nausea	24 (8)	1 (<1)	0	25 (9)	31 (11)	0	1 (<1)	32 (11)	6 (4)	1 (<1)	0	7 (5)
Vaginitis ^b	15 (9)	8 (5)	1 (<1)	24 (15)	10 (6)	7 (4)	1 (<1)	18 (12)	4 (5)	5 (7)	0	9 (12)
Headache	15 (5)	2 (<1)	0	17 (6)	8 (3)	1 (<1)	0	9 (3)	6 (4)	2 (1)	0	8 (6)
Diarrhea	6 (2)	0	0	6 (2)	10 (3)	1 (<1)	0	11 (4)	4 (3)	0	0	4 (3)
Dizziness	5 (2)	1 (<1)	0	6 (2)	10 (3)	0	1 (<1)	11 (4)	1 (<1)	0	0	1 (<1)
Cervicitis ^b	0	4 (3)	1 (<1)	5 (3)	0	2 (1)	1 (<1)	3 (2)	0	2 (3)	1 (1)	3 (4)
Infection	4 (1)	1 (<1)	0	5 (2)	6 (2)	1 (<1)	0	7 (2)	0	1 (<1)	0	1 (<1)
Urethritis ^c	3 (2)	3 (2)	3 (2)	6 (4)	1 (1)	3 (2)	1 (1)	5 (4)	0	1 (2)	0	1 (2)
Vaginal monilliasis ^b	4 (3)	0	0	4 (3)	5 (3)	0	0	5 (3)	1 (1)	0	0	1 (1)
Vomiting	2 (<1)	0	0	2 (<1)	5 (2)	0	0	5 (2)	2 (1)	1 (<1)	0	3 (2)
Pain Abdomen	2 (<1)	0	0	2 (<1)	2 (<1)	2 (<1)	0	4 (1)	3 (2)	0	0	3 (2)

^a All adverse clinical events occurring in $\geq 2\%$ of All Treated Patients.

^b Percentages based on the number of females in the respective treatment group.

^c Percentages based on the number of males in the respective treatment group.

Indication: Uncomplicated Gonorrhoea

Revision Date: 22-Oct-99

Table 11 Drug-Related Adverse Clinical Events, by Severity, All Treated Patients Protocol A1420-012

Adverse Event ^a	Number (%) of Patients														
	Gatifloxacin 400 mg (N = 295)					Gatifloxacin 600 mg (N = 291)					Ofloxacin 400 mg (N = 142)				
	Mild	Mod.	Severe	Very Severe	Total	Mild	Mod.	Severe	Very Severe	Total	Mild	Mod.	Severe	Very Severe	Total
Any Adverse Clinical Event	5 (18)	12 (4)	0	0	6 (22)	56 (19)	1 (7)	1 (<1)	0	76 (26)	2 (16)	4 (3)	0	0	26 (18)
Nausea	2 (8)	2 (<1)	0	0	2 (8)	27 (9)	4 (1)	0	0	31 (11)	5 (4)	1 (<1)	0	0	6 (4)
Headache	1 (4)	3 (1)	0	0	1 (5)	6 (2)	2 (<1)	0	0	8 (3)	3 (2)	3 (2)	0	0	6 (4)
Vaginitis ^b	1 (8)	2 (1)	0	0	1 (9)	6 (4)	4 (3)	0	0	10 (6)	3 (4)	1 (1)	0	0	4 (5)
Diarrhea	5 (2)	1 (<1)	0	0	6 (2)	7 (2)	3 (1)	0	0	10 (3)	4 (3)	0	0	0	4 (3)
Dizziness	5 (2)	0	0	0	5 (2)	10 (3)	0	0	0	10 (3)	1 (<1)	0	0	0	1 (<1)
Moniliasis	4 (3)	0	0	0	4 (3)	2 (1)	3 (2)	0	0	5 (3)	1 (1)	0	0	0	1 (1)
Vaginal ^b															
Somnolence	2 (<1)	2 (<1)	0	0	4 (1)	1 (<1)	1 (<1)	0	0	2 (<1)	2 (1)	0	0	0	2 (1)
Asthenia	1 (<1)	2 (<1)	0	0	3 (1)	2 (<1)	0	1 (<1)	0	3 (1)	1 (<1)	1 (<1)	0	0	2 (1)
Urethritis ^c	2 (1)	1 (<1)	0	0	3 (2)	1 (1)	0	0	0	1 (<1)	0	0	0	0	0
Pain Abdomen	2 (<1)	0	0	0	2 (<1)	2 (<1)	0	0	0	2 (<1)	3 (2)	0	0	0	3 (2)
Vomiting	0	2 (<1)	0	0	2 (<1)	5 (2)	0	0	0	5 (2)	1 (<1)	1 (<1)	0	0	2 (1)
Metrorrhagia ^b	1 (<1)	0	0	0	1 (<1)	1 (<1)	0	0	0	1 (<1)	1 (1)	0	0	0	1 (1)
Fever	0	0	0	0	0	1 (<1)	0	0	0	1 (<1)	2 (1)	0	0	0	2 (1)

^a All drug-related adverse clinical events, ≥ 1% of All Treated Patients.

^b Percentages based on the number of females in the respective treatment group.

^c Percentages based on the number of males in the respective treatment group.

NOTE: Mod. = Moderate.

Indication: Uncomplicated Gonorrhea
Revision Date: 22-Oct-99

The clinical adverse events provided in the datasets were evaluated, particularly to determine what percentage of patients in each of the treatment arm had a diagnosis of vaginal candida infections (as compared to a general nonspecific assessment of vaginitis or vaginitis due to other etiology). The search terms including moniliasis, candida, yeast. Overall, the numbers of patients who fell into these categories were similar between groups.

8.7.2.3.2 LABORATORY TEST ABNORMALITIES

Patients has laboratory testing done pre and post treatment, including hematology, chemistry and urinalysis. Laboratory abnormalities in patients with normal baseline values were uncommon and usually classified as mild. Patients in whom baseline values were abnormal generally did not show a significant change in those values after receiving study drugs, except as would be consistent with a resolving infection. Of note, there was a mild decrease seen in neutrophil counts and white blood cells. Grade 3 abnormalities (refer to complete safety review for definitions) included one patients with neutropenia, one patient with elevated AST and one patients with hyperchloremia in the gatifloxacin 400 mg arm and one patient with neutropenia and another one with hyperbilirubinemia in the gatifloxacin 600 mg. The latter patient was also diagnosed as having hepatitis B infection at entry.

(The following table is from 101 table 12.6.1 of the applicant's submission)

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Table 12. Abnormal Post-Treatment Laboratory Test Values in Patients with Normal Pretreatment Values, All Treated Patients
Protocol A1420-012

	Number (%) of Patients														
	Gatifloxacin 400 mg					Gatifloxacin 600 mg					Ofloxacin 400 mg				
	Na	Grade 1	Grade 2	Grade 3	Grade 4	Na	Grade 1	Grade 2	Grade 3	Grade 4	Na	Grade 1	Grade 2	Grade 3	Grade 4
Hematology															
Hemoglobin	246	7 (3)	1 (<1)	0	0	236	5 (2)	0	0	0	120	3 (3)	0	0	0
WBC	246	15 (6)	2 (<1)	0	0	244	18 (7)	0	0	0	119	8 (7)	0	0	0
Neutrophils	243	25 (10)	6 (2)	1 (<1)	0	228	14 (6)	5 (2)	1 (<1)	0	118	9 (8)	1 (<1)	0	0
Platelets	261	1 (<1)	0	0	0	256	0	0	0	0	124	0	0	0	0
Liver Function															
AST/SGOT	256	10 (4)	0	1 (<1)	0	246	7 (3)	0	0	0	123	8 (7)	0	0	0
ALT/SGPT	256	6 (2)	0	0	0	240	5 (2)	0	0	0	124	4 (3)	0	0	0
Total Bilirubin	261	0	5 (2)	0	0	257	0	3 (1)	1 (<1)	0	130	0	4 (3)	0	0
Alkaline Phosphatase	248	5 (2)	0	0	0	251	5 (2)	0	0	0	121	0	0	0	0
Renal Function															
BUN	272	0	0	0	0	268	0	0	0	0	132	0	0	0	0
Creatinine	269	6 (2)	0	0	0	263	3 (1)	0	0	0	128	3 (2)	0	0	0

Indication: Uncomplicated Gonorrhoea
Revision Date: 22-Oct-99

	Number (%) of Patients															
	Gatifloxacin 400 mg					Gatifloxacin 600 mg					Ofloxacin 400 mg					
	Na	Grade 1	Grade 2	Grade 3	Grade 4	Na	Grade 1	Grade 2	Grade 3	Grade 4	Na	Grade 1	Grade 2	Grade 3	Grade 4	
Metabolic																
Hypoglycemia	17	0	0	0	0	11	0	0	0	0	8	1 (13)	0	0	0	
Hyperglycemia	17	0	0	0	0	11	0	0	0	0	8	0	0	0	0	
Pancreatic Function																
Amylase	250	16 (6)	0	0	0	235	11 (5)	0	0	0	113	5 (4)	0	0	0	
Electrolytes																
Hyponatremia	259	10 (4)	0	0	0	264	4 (2)	0	0	0	129	3 (2)	0	0	0	
Hypernatremia	259		0	0	0	264		0	0	0	129		0	0	0	
Hypokalemia	252	5 (2)	0	0	0	247	3 (1)	0	0	0	121	2 (2)	0	0	0	
Hyperkalemia	252		0	0	0	247		0	0	0	121		0	0	0	
Hypochloremia	266	8 (3)	0	0	0	260	9 (3)	1 (<1)	0	0	128	2 (2)	0	0	0	
Hyperchloremia	266		0	1 (<1)	0	260			0	0	128		0	0	0	
Decreased Bicarbonate	250	13 (5)	0	0	0	245	14 (6)	0	0	0	121	6 (5)	0	0	0	
Increased Bicarbonate	250		0	0	0	245		0	0	0	121		0	0	0	

^a For each test, number of patients with an abnormal pretreatment value who had at least one post-treatment value determined.

Indication: Uncomplicated Gonorrhea
Revision Date: 22-Oct-99

Table 13. Abnormal Post-Treatment Laboratory Test Values in Patients with Abnormal Pretreatment Values, All Treated Patients Protocol A1420-012

	Number (%) of Patients											
	Na	Gatifloxacin 400 mg			Na	Gatifloxacin 600 mg			Na	Ofloxacin 400 mg		
		Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4		Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4		Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4
Hematology												
Hemoglobin	21	2 (10)	0	0	24	2 (8)	1 (4)	0	7	0	0	0
WBC	21	4 (19)	0	0	16	1 (6)	0	0	8	1 (13)	0	0
Neutrophils	24	2 (8)	1 (13)	0	32	4 (13)	1 (3)	0	9	3 (33)	0	0
Platelets	1	0	0	0	1	0	0	0	0	-	-	-
Liver Function												
AST/SGOT	16	0	0	0	23	0	0	0	9	0	0	0
ALT/SGPT	16	0	0	0	29	3 (10)	0	0	8	0	0	0
Total Billrubin	11	0	1 (9)	0	12	0	0	0	2	0	0	0
Alkaline Phosphatase	16	0	0	0	10	0	0	0	9	0	0	0
Renal Function												
BUN	0	-	-	-	1	1 (100)	0	0	0	-	-	-
Creatinine	3	0	0	0	6	0	0	0	4	0	0	0

Indication: Uncomplicated Gonorrhea
Revision Date: 22-Oct-99

	Number (%) of Patients											
	Gatifloxacin 400 mg			Gatifloxacin 600 mg			Ofloxacin 400 mg					
	Na	Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4	Na	Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4	Na	Worsened to Grade 2	Worsened to Grade 3	Worsened to Grade 4
Metabolic												
Hypoglycemia	0	-	-	-	1	1 (100)	0	0	0	-	-	-
Hyperglycemia	0	-	-	-	1	0	0	0	0	-	-	-
Pancreatic Function												
Amylase	22	2 (9)	0	0	34	4 (12)	0	0	19	0	0	0
Electrolytes												
Hyponatremia	13	0	0	0	5	0	0	0	3	0	0	0
Hypernatremia	13	0	0	0	5	0	0	0	3	0	0	0
Hypokalemia	6	0	0	0	1	0	0	0	5	0	0	0
Hyperkalemia	6	0	0	0	1	0	0	0	5	0	0	0
Hypochloremia	6	0	0	0	9	0	0	0	4	0	0	0
Hyperchloremia	6	0	0	0	9	0	0	0	4	0	0	0
Decreased Bicarbonate	22	0	0	0	24	0	0	0	11	0	0	0
Increased Bicarbonate	22	0	0	0	24	0	0	0	11	0	0	0

A For each test, number of patients with an abnormal pretreatment value who had at least one post-treatment value determined.

8.7.3 SUMMARY AND RECOMMENDATIONS:

One clinical trials was conducted. The eradication rates for *Neisseria gonorrhoeae* in bacteriologically evaluable patients from each of the studies is summarized in the table below.

Bacteriological Eradication Rates in Evaluable MALES:

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Urethra	116/117 (99%)	122/122 (100%)	55/55 (100%)
Pharynx	3/3	5/5	1/1
Rectum	0	0	0

COMMENT:

The one patient who had persistence of gonorrhea after treatment with 400 mg gatifloxacin reported reexposure to an infected partner on day 4. While this may therefore represent a reinfection, in the worst case scenario it is included as a persistence.

Bacteriological Eradication Rates in Evaluable FEMALES:

	Gatifloxacin 400 mg PO	Gatifloxacin 600 mg PO	Ofloxacin 400 mg PO
Cervix	100/101 (99%)	103/104 (100%)	55/55 (100%)
Rectum	21/21 (100%)	16/16	8/8
Pharynx	7/7	15/15	3/3

COMMENT:

The bacteriological results presented above indicate that gatifloxacin is 99% effective at each dose in eradicating gonorrhea from the urethra in men and cervix in women. The size of the study meets the recommended number for both men and women.

In addition, the data are adequate to support approval of treatment of rectal gonorrhea in women. However, there are no data on the treatment of rectal gonorrhea in males.

The information on pharyngeal gonorrhea treated with 400 mg PO (the proposed dosing regimen) is marginal for both males and females and therefore should not be approved. Interestingly enough, one could make an argument that the 600 mg regimen is supported by the data from 22 patients (7 at 400 mg, 15 at 600 mg) treated with gatifloxacin;

however, proposing a 400 mg dose for genital and rectal sites and 600 mg for pharyngeal site may lead to confusion in prescribing. More data on pharyngeal isolates treated with the 400 mg regimen would be useful.

These results support approval of gatifloxacin for the treatment of uncomplicated gonorrhea -- cervical and urethral, as well as rectal gonorrhea in females -- at a dose of 400 mg, as requested by the applicant. Data on the effectiveness of the 400 mg dose for pharyngeal gonorrhea was inadequate (see tables above).

The applicant has provided information on the rate of beta-lactamase producing *N. gonorrhoeae* isolates from the trial, but, in keeping with the regulatory policy on this subject, has not requested any labeling statements about that group of isolates, because this mechanism of resistance is not linked to resistance to quinolones. None of the quinolones approved for the treatment of gonorrhea have included any comments relative to beta-lactamase production.

8.7.4 PROPOSED LABELING REVISION:

The INDICATIONS AND USAGE section of the proposed package insert, relative to the indication of gonorrhea, should be revised to read:

Uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae*.
Acute, uncomplicated rectal infections in women due to *Neisseria gonorrhoeae*.
(See WARNINGS.)

NOTE: The efficacy of gatifloxacin in treating male patients with rectal infections and male or female patients with pharyngeal infections caused by *N. gonorrhoeae* has not been established.

Information on other quinolones is presented below. Examples of granting gender-specific site indications is also listed.

8.7.5 QUINOLONES APPROVED FOR GONORRHEA:

Noroxin:	Sexually Transmitted Diseases (See WARNINGS. *) Uncomplicated urethral and cervical gonorrhea due to <i>Neisseria gonorrhoeae</i> .
Enoxacin:	Sexually Transmitted Diseases (See WARNINGS. *) Uncomplicated urethral and cervical gonorrhea due to <i>Neisseria gonorrhoeae</i> .
Ciprofloxacin:	Sexually Transmitted Diseases (See WARNINGS. *) Uncomplicated urethral and cervical gonorrhea due to <i>Neisseria gonorrhoeae</i> .

Ofloxacin: Acute uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae*. (See WARNINGS.*)

Trovafloxacin: Indication withdrawn due to risk/benefit

Grepafoxacin: Uncomplicated gonorrhea (urethral in male and endocervical and rectal in females) caused by *Neisseria gonorrhoeae*. (See WARNINGS.*)

*The last paragraph in the WARNINGS section for these products states that the respective quinolone is not effective in the treatment of syphilis, etc.

QUINOLONES NOT INDICATED FOR GONORRHEA TREATMENT:

lomefloxacin
levofloxacin
sparfloxacin
cinoxacin
trovafloxacin

8.7.6 LABELING EXAMPLES FOR RECTAL AND/OR PHARYNGEAL SITES:

Cefpodoxime proxetil:

Acute, uncomplicated urethral and cervical gonorrhea caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains). Acute, uncomplicated ano-rectal infections in women due to *Neisseria gonorrhoeae* (including penicillinase-producing strains). NOTE: The efficacy of cefpodoxime in treating male patients with rectal infections caused by *N. gonorrhoeae* has not been established. Data do not support the use of cefpodoxime proxetil in the treatment of pharyngeal infections due to *N. gonorrhoeae* in men or women.

Ceftin:

UNCOMPLICATED GONORRHEA, urethral and endocervical, caused by penicillinase-producing and non-penicillinase-producing strains of *Neisseria gonorrhoeae* and uncomplicated gonorrhea, rectal, in females, caused by non-penicillinase-producing strains of *Neisseria gonorrhoeae*.

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- cc: NDA 21-061
- HFD-590
- HFD-590/MO/Korvick
- HFD-590/DepDir/Albrecht
- HFD-520/Pharm/Ellis
- HFD-520/Micro/Altaie
- HFD-590/Chem/
- HFD-590/CSO/Atkins
- Clinical Review GC

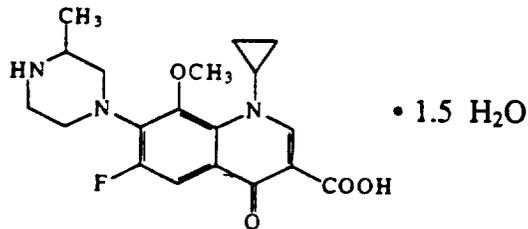
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Medical Officer Review of NDA 21-061 and 21-062: Gatifloxacin (Tequin™)

Date Submitted: 28 December 1998
Date Received: 29 December 1998
Date Assigned: 29 December 1998
Date Completed: 21 December 1999

Applicant: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, Connecticut 06492
203-677-6883
Contact person: Douglas Kriesel, Ph.D.

Drug: Proprietary name - Tequin™
Generic name - Gatifloxacin
Chemical name - (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolone carboxylic acid sesquihydrate
Molecular formula - C₁₉H₂₂FN₃O₄ • 1.5 H₂O
Molecular weight - 402.42 (sesquihydrate)
Molecular structure -



Drug Class: 8-methoxyfluoroquinolone antibacterial

Formulation: (capsule, suspension, lyophilized powder, etc.)

Route of administration: Oral; 200 mg and 400 mg tablets

Related NDA: 21-062, 21-061

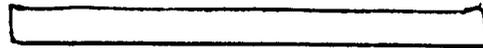


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9.0 INTEGRATED SUMMARY OF SAFETY

The safety evaluation in BMS-sponsored trials includes 586 patients from clinical pharmacology studies and 6198 patients from 15 efficacy trials. Two clinical pharmacology studies had active controls, study AI420-015 used ciprofloxacin and AI420-032 used both lomefloxacin and ciprofloxacin. Six other clinical pharmacology trials were placebo-controlled. Overall, 475 patients received gatifloxacin, 307 as a single dose and 168 as multiple doses. IV gatifloxacin was administered to 28 patients. The cut off for this safety analysis was 30-Sep-98.

In the efficacy trials, the largest experience was with a dose of 400 mg once a day given either orally (PO) (3021 patients) or intravenously (IV) followed by PO (165 patients). The duration of treatment was usually 7 to 14 days, with shorter courses of therapy given in two studies (AI420-010 and -012). The 200 and 600 mg PO doses were administered to 443 and 291 patients, respectively.

The total numbers of patients exposed to gatifloxacin in the Bristol-Myers Squibb Pharmaceutical Research Institute, efficacy trials is as follows:

Gatifloxacin 200 mg PO: 443 patients,

Gatifloxacin 400 mg PO: 3,021 patients,

Gatifloxacin 600 mg PO: 291 patients,

Gatifloxacin 400 mg IV-PO switch: 165 patients.

Total exposed to Gatifloxacin at any dose in the clinical efficacy trials = 3,920 patients compared to 2,278 patients exposed to comparator treatments.

In addition, the applicant supplied limited safety data from its' partner organizations Kyron, Japan [redacted]. The database from Kyron, Japan was analyzed earlier this year and information on 2,782 patients exposed to gatifloxacin is presented. The information from the [redacted] group was still under analysis at the time of the safety update, the experience there was based upon 7 phase III, double blind, efficacy trials which accrued 3,894 patients.

9.1 Adverse Clinical Events

The applicant provided an integrated summary of adverse clinical events according to dose administered. The FDA review paralleled this approach. In addition, a truly integrated summary, across all doses, was performed with regard to the potential events that are related to the quinolone drug class.

Safety in Normal Volunteers: Pharmacokinetic Studies

Few adverse events were reported in the clinical pharmacology studies conducted in volunteers. Overall, there were limited differences between the gatifloxacin group, the active comparator group, and the placebo group.

The following tables list several categories for adverse clinical event, where the events were the most frequent or of interest to the FDA.

Selected Adverse Events of All Cause, Studies in Volunteers			
No. (%) of Patients			
Adverse Event	Gatifloxacin N=475	Active Comparator N=40	Placebo N=71
Headache	65 (14)	5 (13)	6 (8)
Nausea	45 (9)	3 (8)	3 (4)
Dizziness	34 (7)	5 (13)	7 (10)

The most frequent events appear to be headache, nausea and dizziness. Adverse clinical events were generally mild in nature (see table below). There were three severe adverse clinical events in the gatifloxacin group: headache, IV site reaction, and vomiting occurred in a single patient each. The IV site reaction consisted of redness and induration extending to most of the arm above the injection site. It appears that the severity of the local IV reactions were dependant on the gatifloxacin concentration that was used in the infusion. The event occurred at a concentration that will not be recommended for the marketed product.

Selected Adverse Events of All Causes by Severity, Studies in Normal Volunteers									
No. (%)									
Adverse Events	Gatifloxacin N= 475			Comparator N=40			Placebo N=71		
	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Headache	44 (9)	20 (4)	1 (<1)	1 (2)	4 (10)	--	4 (6)	2 (3)	--
Nausea	38 (8)	7 (1)	--	1 (2)	2 (5)	--	2 (3)	1 (1)	--
Dizziness	32 (7)	2 (<)	--	3 (7)	2 (5)	--	4 (6)	3 (4)	--

Gatifloxacin Selected Adverse Events and Duration of Therapy . Studies in Normal Volunteers		
No. (%) Patients		
Adverse Events	Single Dose N=307	Multiple (5-14) Doses N=168
Headache	46 (15)	19 (11)
Nausea	23 (7)	22 (13)
Dizziness	16 (5)	18 (11)
Puritus	2 (1)	20 (12)

There were some differences between patients receiving a single dose of gatifloxacin and those receiving between 5 and 14 doses; nausea, dizziness, IV site reaction and puritus tended to be higher with longer duration of therapy. Again these events were mild for the most part.