May 1, 2006

Andrew von Eschenbach, MD, Acting Commissioner
US Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

Public Citizen, representing more than 100,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. Section 355(e)(3) and 21 C.F.R. 10.30, to immediately ban the widely prescribed fluoroquinolone antibiotic gatifloxacin (Tequin, Bristol-Myers-Squibb—1.2 million prescriptions filled in 2005) because of the increased risk of dysglycemia (hypoglycemia [low blood sugar] and hyperglycemia [high blood sugar]) in humans. Gatifloxacin was approved for use in the United States in December of 1999. According to our analysis, there have been 388 patients with gatifloxacin-associated dysglycemia, including 20 deaths and 159 hospitalizations, reported to the FDA from January 1, 2000, through June 30, 2005. The fourth label change of February 15, 2006 was an insufficient remedial action for a drug that we will show carries unique risk without unique clinical benefit compared to the 7 other fluoroquinolones currently approved by the FDA and other drugs approved for similar indications. Bristol-Myers-Squibb's quiet announcement last Friday that it would no longer manufacture Tequin for economic reasons is similarly inadequate to protect the public's health since they apparently have no intention, absent FDA action to ban the drug, to stop selling the large amount of Tequin already in the channels of commerce. Thus, without an FDA ban, thousands of additional patients will be prescribed this unacceptably dangerous drug.

Gatifloxacin is indicated for the treatment of acute exacerbations of chronic bronchitis, acute sinusitis, community-acquired pneumonia, uncomplicated urinary tract infection, complicated urinary tract infection, pyelonephritis, and uncomplicated urethral and cervical gonorrhea. Other drugs to treat these conditions do not have the risks of gatifloxacin. When this drug is banned, it will be the fifth drug out of 13 approved in this class to be taken off the market because of serious safety problems. The banned quinolone antibiotics are temafloxacin (because of hypoglycemia, renal failure, and hemolytic anemia)[1,2] grepafloxacin and sparfloxacin (because of QT-interval prolongation and increased risk of heart arrhythmias),[3,4,5] and trovafloxacin (because of liver toxicity).[6,7]
Public Citizen's concern is based on the following information: 1) the relatively high numbers and rates (compared to other fluoroquinolones and/or antibiotics with similar indications) of gatifloxacin-associated dysglycemia Adverse Event Reports (AERs) calculated from data collected by the US FDA's Adverse Event Reporting System (AERS)

and Health Canada's Adverse Drug Reaction Monitoring Program (CADRMP) [i]; 2) a study by Park-Wyllie, et al published on March 1, 2006, in the *New England Journal of Medicine (NEJM)* that showed that all patients (diabetic and non-diabetic, combined) receiving gatifloxacin had approximately 17 times the odds of having a hyperglycemic episode and 4 times the odds of having a hypoglycemic episode compared to those taking macrolide antibiotics (e.g. erythromycin);[8] and 3) the relatively high numbers and rates (compared to other fluoroquinolones and/or antibiotics with similar indications) of gatifloxacin-associated dysglycemic events in the manufacturer's safety studies in uninfected patients and other studies in infected patients including: clinical trials, cohort studies, case-control studies (including the study above), post-marketing surveillance studies, and case reports.

Public Citizen's Analysis of Gatifloxacin-Associated Dysglycemia AERs Submitted to the US FDA from January 1, 2000 to June 30, 2005

We searched the FDA's AERS Database from January 1, 2000, to June 30, 2005, for all AERs in which gatifloxacin, levofloxacin, moxifloxacin, or azithromycin were "primary suspect" drugs. To account for the Weber effect (the increased reporting of AERs in the first few years after approval of a drug), we chose drugs that had similar FDA-approval dates: gatifloxacin (1999), moxifloxacin (1999), levofloxacin (1996), and azithromycin (1996). We were aware that because none of the comparator drugs had FDA approval dates *after* the year of gatifloxacin's approval (1999), there was a potential introduction of bias. Consequently, we performed the same analysis on telithromycin (Ketek), a macrolide antibiotic that was approved in 2004; however, this drug was not included in the final analysis. [ii] The database included spontaneous reports received between January 1, 2000, and June 30, 2005 (the last period for which we have data). We removed any reports that did not have a manufacturing number (MN) and all duplicate reports.

A dysglycemia AER was defined as having one or more of the following adverse reaction (MedDRA) terms: hyperglycaemia, hypoglycaemia, diabetic coma, diabetic hyperglycaemic coma, diabetic hyperosmolar coma, diabetic hyperosmolar nonketoacidosis, diabetic ketoacidosis, hyperosmolar state, hypoglycaemic coma, and nonketotic hyperglycaemic-hyperosmolar coma. Fatal dysglycemia events were defined as dysglycemia AERs with the outcome of "death." Because there may have been multiple reports with different outcomes but having the same MN, a hierarchy was established to select the report with the worst outcome. Using the standard outcome codes from AERS,

[i] Health Canada's CADRMP uses the term "Adverse Reaction Report" (ARR) instead of the term "Adverse Event Report" (AER) used by the US FDA.

[ii] Telithromycin was approved by the FDA in 2004. Because of its relatively recent approval, we performed the above analysis using data collected over a 1 year time period; consequently, although the numbers and rates may be meaningful independently, it was not epidemiologically appropriate to compare them to those of the other drugs (which were calculated using data collected over a five year time period). Therefore, telithromycin was not included in the final analysis. We searched the FDA's AERS Database from June 30, 2004, to June 30, 2005, for all AERs in which telithromycin was a "primary suspect" drug. Seven telithromycin-associated dysglycemia AERs were found (4 hypo- and 3 hyperglycemia). The total number of prescriptions filled from June 30, 2004, to June 30, 2005, was 2646699. The rate of dysglycemia AERs per million Rx was 2.6 (1.5 for hypo- and 1.1 for hyperglycemia). The number of dysglycemia AERs with death as outcome was 2, and the rate of dysglycemia AERs with death per million Rx was 0.8. half the rate for gatifloxacin despite the recent introduction of telithromycin into the market.

the hierarchy was as follows: death > life threatening > disability > hospitalization > required intervention. (For instance, if there were 3 AERs with the same MN yet different outcomes, death, hospitalization, and required intervention, the report with the outcome "death" was selected and the others deleted). If multiple reports with the same MN had the same outcome, the report with the earliest FDA receipt date was selected.

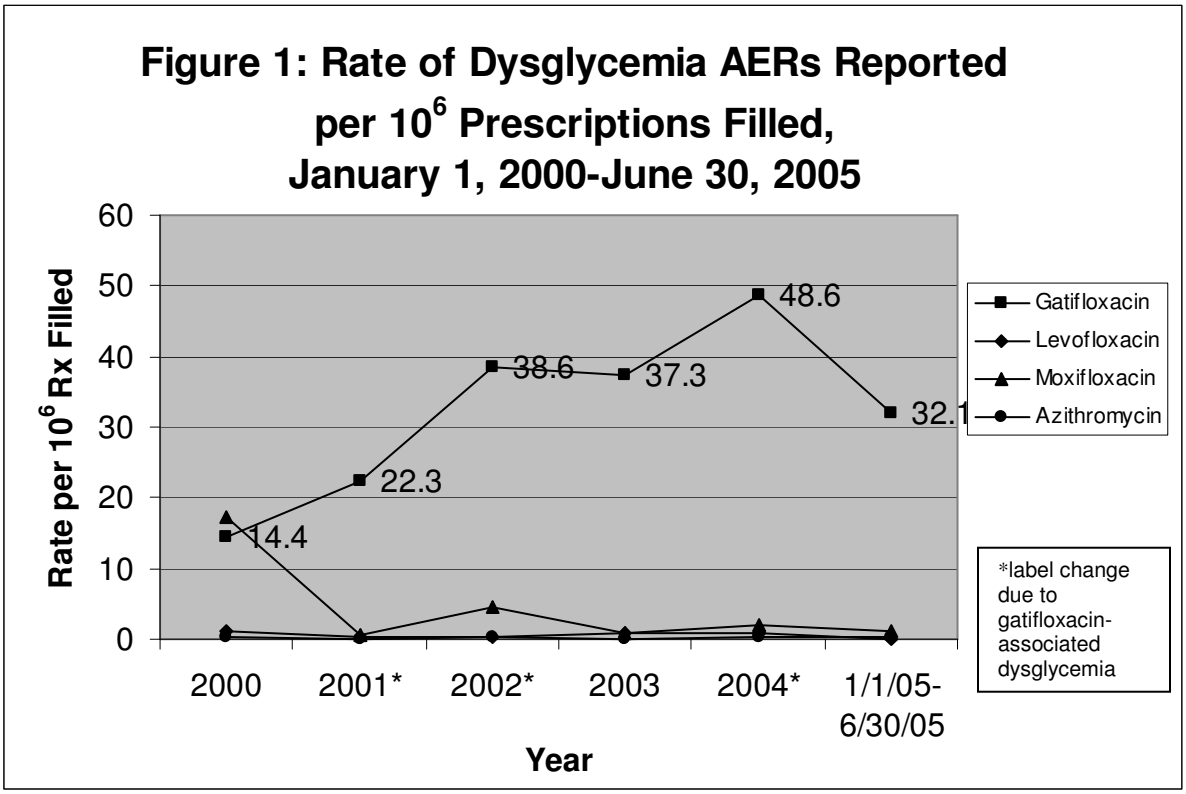
A limitation of these data is that adverse events are significantly under-reported to the FDA; therefore, the numbers of actual gatifloxacin AERs are probably significantly higher than indicated by the FDA data. The denominators used to calculate rates were acquired from IMS data that provided the "total number of prescriptions filled" by year for all of the drugs being evaluated.

Table 1. Frequency/Rate of Dysglycemia AERs by Category, January 1, 2000-June 30, 2005

Variable	Gatifloxacin	Levofloxacin	Moxifloxacin	Azithromycin
NDA Approval Year	**1999**	1996	1999	1996
Total No. Dysglycemia AERs	**388**	41	35	41
No. Hyperglycemia AERs	**132**	8	13	13
No. Hypoglycemia AERs	**256**	33	22	28
Total No. Rx Filled 1/1/00-6/30/05	**12139627**	72387476	11856655	205388036
Rate of Dysglycemia AERs per 10^6 Rx	**32.0**	0.6	3.0	0.2
Rate of Hyperglycemia AERs per 10^6 Rx	**10.9**	0.1	1.1	0.1
Rate of Hypoglycemia AERs per 10^6 Rx	**21.1**	0.5	1.9	0.1
No. Dysglycemia AERs w/ Death as Outcome	**20**	4	1	0
Rate of Dysglycemia AERs w/ Death per 10^6 Rx	**1.6**	0.1	0.1	0

It can be seen from Table 1 and Figure 1 (above) that from January 1, 2000, to June 30, 2005, gatifloxacin has the highest *number* of total dysglycemia AERs (and those with death as the outcome) and the highest *rate* of total dysglycemia AERs (and those with death as an outcome) per million prescriptions filled. The rate of gatifloxacin-associated dysglycemia AERs per million prescriptions is 11 times that of moxifloxacin (which had the second highest rate among drugs studied), and the rate of gatifloxacin-associated dysglycemia AERs with death as an outcome per million prescriptions is 16 times higher than that of moxifloxacin (which had the second highest rate among drugs studied). Of the 20 gatifloxacin-associated dysglycemia AERs with death as an outcome, 8 listed hyperglycemia and 12 listed hypoglycemia as the primary reaction term.

Figure 1 below shows the rates of reports of dysglycemia AERs per million prescriptions filled over time. With the exception of 2000, gatifloxacin consistently had higher rates than all the other drugs in each year.



Other Analyses of Gatifloxacin-Associated Dysglycemia AERs and ARRs from the US FDA and Health Canada's CADRMP, respectively.

This section focuses on adverse event reporting for gatifloxacin-associated dysglycemia from the following sources: BMS Phase II/III AERs submitted to the FDA, Frothingham, et al's evaluation of AERs submitted to the FDA, and Health Canada's evaluation of "adverse reaction reports" submitted to the CADRMP.

An evaluation of the manufacturer's safety database for the Phase II/III trials revealed that 7 episodes of hypoglycemia (there were no gatifloxacin-associated hyperglycemia AERs submitted) were reported as an adverse event by investigators: 6/3920 in patients treated with gatifloxacin and 1/2278 in the clarithromycin-treated group (relative risk 3.49; 95% CI, 0.4-29; p=0.43).[9,10] Of the 6 patients with gatifloxacin-associated hypoglycemia, 5 were diabetic; however, the non-diabetic patient was clinically symptomatic and had a glucose value of 33 mg/dl on day 2 of gatifloxacin therapy. The medical officer reported that [for this non-diabetic patient], "the reason for this symptomatic hypoglycemia episode is unknown."

Frothingham, et al's study entitled "Glucose Homeostasis Abnormalities Associated with Use of Gatifloxacin," published on November 1, 2005, in *Clinical Infectious Diseases,* evaluated dysglycemia AERs in FDA's database associated with the use of ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin reported between November 1, 1997 and September 24, 2003.[11] The use of gatifloxacin was associated with 47.7 dysglycemia AERs per million retail prescriptions, much higher than with ciprofloxacin (0.4 dysglycemia

AERs per million retail prescriptions), levofloxacin (1.1 dysglycemia AERs per million retail prescriptions), and moxifloxacin (3.9 dysglycemia AERs per million retail prescriptions) (P<0.0001 for each comparison between gatifloxacin and other quinolones). The rate for gatifloxacin-associated dysglycemia AERs per million retail prescriptions is approximately 12 times that of moxifloxacin (the second highest rate among drugs studied). The use of gatifloxacin was associated with 1.8 dysglycemia AERs with the outcome of death per million retail prescriptions, higher than with ciprofloxacin (0.04 dysglycemia AERs with the outcome of death per million retail prescriptions), levofloxacin (0.1 dysglycemia AERs with the outcome of death per million retail prescriptions), and moxifloxacin (0) (P<0.001 for each comparison between gatifloxacin and other quinolones). The rate for gatifloxacin-associated dysglycemia AERs with the outcome of death per million retail prescriptions is approximately 18 times that of levofloxacin (the second highest rate among drugs studied).

There are three possibilities (assuming our denominators are comparable) that explain why the "rates of dysglycemia AERs per million prescriptions" and "dysglycemia AERs with the outcome of death per million prescriptions" were lower in Public Citizen's analysis than in Frothingham's. (We have emailed and telephoned the author, but have been unable to communicate with him). (1) Frothingham's study covered an earlier time period than in the PC analysis. (2) The author states in the *Methods* section that cases were sorted by "report number" and duplicates were removed. It is unclear whether he is referring to the Individual Safety Report (ISR) number or Manufacturing Number (MN), but for any given drug, there are certainly more AERs with unique ISRs than there are AERs with unique MNs. This is because each adverse event has a unique ISR while there is only one MN per patient; therefore, a given patient with multiple adverse events will have multiple AERs with a common MN and multiple, unique ISRs. (3) The author reports he included AERs that listed 1 of the above 4 quinolones as a primary or secondary suspect drug, whereas our analysis included only primary suspect drugs. Given these systematic methodological differences, we would expect the rates of gatifloxacin-associated dysglycemia AERs (and those with the outcome of death) per million prescriptions to differ between Public Citizen's and Frothingham's analysis; however, these differences should not introduce bias into the comparison with the other drugs because calculating the relative risks comparing these rates (between gatifloxacin and comparator study drug) within each analysis should essentially control for the aforementioned differences.

Health Canada has received 28 reports of gatifloxacin-associated dysglycemia (44% of total reports received for the drug) from February 21, 2001, (the date marketed in Canada) to February 28, 2003. Of the 28 reports, 19 designated hypoglycemia, 7 designated hyperglycemia and 2 designated both hypoglycemia and hyperglycemia.[12] Hypoglycemic reactions most frequently occurred within 24 hours and usually within 72 hours after the start of therapy. Hyperglycemic reactions most frequently occurred after 4 to 10 days. (These temporal effects of gatifloxacin on blood glucose [i.e. early hypoglycemia and/or later hyperglycemia] are consistent with manufacturer-sponsored safety and post-marketing studies.)

Manufacturer-Sponsored Human Volunteer Studies in Uninfected Patients

In this analysis, we rate the relative importance of each study by describing its "level of evidence" as categorized by the Oxford Centre for Evidenced Based Medicine[13] (see Table 10).

As a result of the preclinical trials suggesting a causal relationship between gatifloxacin and dysglycemia, the manufacturer performed 4 studies (three prior to approval and one after approval) in uninfected volunteers to evaluate the effects of gatifloxacin on glucose homeostasis (see Table 2 below). [14,15] The FDA reviewer's comments and manufacturer's note (from the 2004 Tequin Package Insert) show that gatifloxacin had transient effects on blood glucose and may have affected serum insulin levels; furthermore, the study participants in the gatifloxacin arm in all 4 studies demonstrated the pattern of early hypoglycemia followed by later hyperglycemia. An excerpt from the revised 2004 Tequin Package insert supports this temporal relationship of early hypo- and later hyperglycemia:

> Studies conducted in non-infected patients with type II diabetes mellitus controlled on oral hypoglycemic agents have demonstrated that Tequin is associated with disturbances in glucose homeostasis including an increase in serum insulin and decrease in serum glucose usually following administration of initial doses (i.e., first 2 days of treatment), and sometimes associated with symptomatic hypoglycemia. Increases in fasting serum glucose were also observed, usually after the third day of Tequin administration, continuing throughout the duration of treatment, and returning to baseline by 28 days after the cessation of gatifloxacin treatment in most patients.[16]

Table 2 on the next page summarizes the three manufacturer-sponsored pre-approval and one post-approval studies performed to evaluate gatifloxacin's effect on glucose metabolism. All of the comments suggested that gatifloxacin may affect insulin production/distribution and/or glucose metabolism. Note: Study AI420-025 was in non-diabetic patients.

Table 2. BMS-Tequin Safety Studies to Evaluate Glucose Homeostasis			
Study No.	**Study Participants**	**Study Description**	**Comments**
Phase I AI420-032 n=48	Healthy, type II diabetics controlled with diet and exercise	Randomized, double-blind, placebo-controlled trial comparing gatifloxacin 400 mg QD, ciprofloxacin 500 mg BID, and placebo	**FDA Medical Officer (MO):** "There was a slight increase in fasting insulin on Day 1 with a decrease in fasting glucose which was not found on subsequent days." "An acute effect of gatifloxacin on insulin release could not be ruled out."
Phase I AI420-036 n=32	Healthy, type II diabetics controlled with glyburide	Randomized, double-blind, placebo-controlled trial comparing gatifloxacin 400 mg QD and placebo	**FDA MO:** "A modest decrease in insulin production with multiple dose administration could not be ruled out."
Phase I AI420-025 n=N/A	Healthy, non-diabetics	Randomized, double-blind, placebo-controlled trial comparing multiple doses of gatifloxacin from 200-800 mg QD and placebo	**FDA MO:** "There was a transient decrease in serum glucose at all dose levels at the one hour time point on Day 1 with a prompt recovery by the end of the second hour."
Phase IV Tequin Package Insert, 2002 n=70	Healthy, type II diabetics controlled with oral hypoglycemic drugs	Randomized, double-blind, placebo controlled trial comparing gatifloxacin 400 mg QD and placebo	**Manufacturer's Note:** "transient moderate increases in serum insulin and decreases in serum glucose conc. were noted with the first dose and resulted in symptomatic hypoglycemia in some subjects in the glyburide treated group, particularly on the first day of therapy. Increases in fasting glucose (average increases of 40 mg/dL) were noted after day 3 in both the glyburide and non-glyburide-treated groups, which returned to baseline by day 28."

All four of these studies were randomized controlled trials (RCTs), which are considered the highest level of evidence, Level 1 (see Table 10). While the FDA MO did not mention if the differences in serum insulin/glucose levels between the gatifloxacin and control arms in these studies were statistically significant, it is clear that there is a trend toward gatifloxacin-associated dysglycemia. It is important to realize that the sizes of the study populations in these studies may have been too small to detect any statistically significant differences in rates of dysglycemia.

Studies in Infected Patients

Clinical Trials. The manufacturer sponsored an RCT by Gajjar et al that compared the effects of gatifloxacin and ciprofloxacin on glucose homeostasis in 48 patients with diabetes. Patients were randomly assigned to receive gatifloxacin 400 mg/day orally, ciprofloxacin 500 mg twice/day orally, or placebo for 10 days. The authors reported that fasting glucose levels 0-6 hours after gatifloxacin administration on days 1 and 10 showed a "downward trend" but that this was not statistically significant. Furthermore, gatifloxacin use was associated with a transient, short-term increase in insulin release.[17] It is important to note that there were only 48 subjects in the trial; therefore, it might not have been powered adequately to detect statistically significant differences.

Two RCTs reported higher rates of hyperglycemia with gatifloxacin compared to comparator drugs. A study by Correa, et al reported that of 27 patients with normal baseline

glucose values, hyperglycemic events occurred in 3/17 (17.6%) and 1/10 (10.0%) of gatifloxacin- and ceftriaxone-treated patients, respectively.[18] A study by Mendoca et al in 56 patients reported that hyperglycemic events occurred in 1/29 (3.4%) and 0/27 (0%) of gatifloxacin- and ceftriaxone-treated patients, respectively.[19] However, none of these results from the two studies were statistically significant.

An RCT by Cannon, et al randomly assigned 4162 hospitalized patients with acute coronary syndromes to gatifloxacin or placebo for presumptive treatment of Chlamydia pneumoniae for secondary prevention of cardiac events. At 30 days post-treatment with either gatifloxacin or placebo, among patients who did not have diabetes at baseline, new-onset diabetes (defined as the presence of one or more non-fasting serum glucose values of greater than or equal to 200 mg/dl, two or more non-fasting serum glucose values of greater than or equal to 140 mg/dl, or two or more fasting serum glucose values of greater than or equal to 126 mg/dl) tended to develop more frequently in patients treated with gatifloxacin than in those given placebo (4.6 percent vs. 3.4 percent, P=0.08). Among patients with diabetes, there were trends toward more patients who were treated with gatifloxacin having episodes of hyperglycemia than patients who were treated with placebo (30.7 percent vs. 25.4 percent, P=0.11) and toward more patients who were treated with gatifloxacin having episodes of hypoglycemia (2.6 percent vs. 1.5 percent, P=0.32).[20]

All 4 of these studies are RCTs. The studies by Gajjar, Correa, and Mendoca may have been too small to detect statistically significant differences in rates of dysglycemic events. In contrast, the large study by Cannon did detect a statistically significant difference in rates of new-onset diabetes in gatifloxacin versus placebo.

Cohort Studies. The manufacturer reported safety data for 166 patients (enrolled in pre-approval trials) who had been tested for *fasting* blood glucose (FBG) and had normal baseline levels. Hyperglycemia and hypoglycemia were defined as serum glucose greater than 110 mg/dl and less than 60 mg/dl, respectively. Of 166 patients, 14 (8%) developed hyperglycemia and 2 (1.2%) developed hypoglycemia.[21]

Because all of the gatifloxacin-associated dysglycemia AERs reported in the pre-approval trials were for hypoglycemia (7/7—see Adverse Event Reporting Section), the manufacturer searched its patient database to identify 4733 patients enrolled in pre-approval clinical trials for whom glucose levels (*fasting and non-fasting*) were available both pre- and either during or post-treatment. Potential hypoglycemia was defined as a serum glucose (fasting or non-fasting) below 60 mg/dl. Of 4733 patients, 79 developed hypoglycemia, "translating to an incidence of 1.7% in the gatifloxacin group, 1.4% in patients treated with other quinolones, and 1.8% in the patients treated with other antibiotics" (the numbers of hypoglycemic events for each group were not given). Furthermore, among 3000 gatifloxacin treated patients, 4 had serum glucose levels below 40 mg/dl compared to 0/1183 in the other quinolone group and 1/550 in the non-quinolone group.[22]

To further assess the potential dysglycemic effects of gatifloxacin, the manufacturer analyzed safety data (see Table 4 below) from their Tequin Clinical Experience Study (TeqCES). This was a Phase IV, open-label trial involving 15,000 Canadian patients from

2000-02 that was designed primarily to evaluate bacterial susceptibility patterns in the context of community-acquired pneumonia treatment.[23] Of non-diabetic patients who took gatifloxacin, 0.007% and 0.03% had hyperglycemic and hypoglycemic events, respectively. Of diabetic patients who took gatifloxacin, 1.3% and 0.64% had hyperglycemic and hypoglycemic events, respectively. Of all patients who took gatifloxacin, 0.03% had either a hyperglycemic or hypoglycemic event (all reversible with appropriate management, which included discontinuation of gatifloxacin therapy).[24] It is interesting to note that in this study, the rate of dysglycemic events for all patients (300 per million patients) is approximately 10 times the rate of gatifloxacin-associated dysglycemia AERs (32 per million prescriptions) from Public Citizen's analysis. (10% is the high-end adverse event reporting rate estimate [i.e. 1-10%] usually used by the FDA.)[25]

Table 4. BMS-Canada Post-Marketing Study to Evaluate Gatifloxacin-Associated Dysglycemia

Type of Dysglycemic Event	Non-Diabetic		Diabetic		All Patients, both types of dysglycemic events	
	% of Pts w/ Events	per 10^6 Patients	% of Pts w/ Events	per 10^6 Patients	% of Pts w/ Events	per 10^6 Patients
Hyperglycemic Events	0.007	70	1.3	13000	**0.03**	**300**
Hypoglycemic Events	0.03	300	0.64	6400		

Another cohort study by Greenberg et al reported an association between gatifloxacin and hypoglycemia 48 hours after therapy initiation. Hypoglycemia was defined as a serum glucose less than or equal to 60 mg/dl within 48 hours after the first dose of the antibiotic. The gatifloxacin cohort was compared to a cohort receiving non-quinolone drugs. The authors reported that 5/50 (10%) patients receiving gatifloxacin and 1/89 (1.1%) patients receiving non-fluoroquinolone antibiotics had hypoglycemia (P=0.041, by z test).[26]

Cohort studies are considered Level 2 evidence (see Table 10). In the manufacturer-sponsored study in 4733 patients, the percentage of gatifloxacin-treated patients who developed hypoglycemia is high (given that the group with the highest percentage of hypoglycemic events in the TeqCES study was 1.3% in diabetics), regardless of the fact that the percentages are high in the other two groups; however, it is unclear why the percentages in these other groups are also high. We do not know the patient characteristics in each of the treatment arms, as the manufacturer's analysis was non-randomized. If the prevalence of diabetes and/or use of oral hypoglycemics/insulin were significantly higher in the non-fluoroquinolone arm, we might see the results that we did. The incidence estimates for dysglycemic events in the TeqCES study are more likely to be accurate given the larger population size.

Case-Control Studies. A nested-case control trial by Mohr et al evaluated dysglycemic events in 17,108 patients who received either a fluoroquinolone or ceftriaxone; of these, 101 received levofloxacin, gatifloxacin, or ceftriaxone and also had serum glucose concentrations above 200 or below 50 mg/dl within 72 hours of receiving the drug. Dysglycemia rates relative to treatment were as follows: gatifloxacin 76/7540 (1.01%), levofloxacin 11/1179 (0.93%), ceftriaxone 14/7844 (0.18%), ciprofloxacin 0/545 (0%), and any fluoroquinolone 87/9264 (0.94%). Dysglycemia was more likely to occur in patients receiving any fluoroquinolone than in those receiving ceftriaxone (Odds Ratio [OR] 3.32, 95% confidence interval (CI) 2.31-4.78, $p < 0.05$). The rate of gatifloxacin-associated

dysglycemia did not differ from that of levofloxacin (OR 1.07, 95% CI 0.62-1.86, p = 0.8), but this result was not statistically significant.[27]

A nested case-control study by Graumlich et al evaluated hypoglycemic events in 7,287 hospitalized patients who received gatifloxacin or levofloxacin therapy; of these 113 received gatifloxacin or levofloxacin and had blood glucose levels below 51 mg/dl. The 12-month incidence of hypoglycemia was 11/1000 for patients on levofloxacin and 21/1000 for patients on gatifloxacin (absolute risk increase 10/1000 patients, 95% confidence interval [CI] 4-16/1000). Renal failure, sepsis, and concomitant hypoglycemic drug therapy significantly predicted hypoglycemia. After adjustment for these significant predictors, the odds of having hypoglycemia were 2.81 (95% CI 1.02-7.70) times higher after gatifloxacin than levofloxacin therapy; this result was statistically significant.

One case-control study by Lomaestro et al reported an association between gatifloxacin and hypoglycemia on day 1 after therapy initiation. [28] Of 335 patients who received either gatifloxacin or piperacillin-tazobactam (PT), 216 were identified with pre-antibiotic serum glucose between 65 and 140 mg/dl. On day 1 after therapy initiation, 7/134 (5.3%) of gatifloxacin treated and 0/82 (0%) of PT-treated patients had serum glucose below 65 mg/dl (p=0.04).

Arguably, the most important study in this petition (because of its high statistical power and sound methodology) is the recent study by Park-Wyllie et al.[29] This consisted of two population-based nested case-control studies that examined dysglycemia-related health outcomes associated with various antibiotics in a population of approximately 1.4 million Ontario, Canada residents over 65 (see Table 5 below). 788 and 470 patients were identified who were treated for hypoglycemia and hyperglycemia within 30 days after antibiotic therapy, respectively. [iii]

The authors adjusted for conditions that might influence or be reflective of glycemic control, including liver disease, renal insufficiency, and alcohol abuse, as well as the number of hospital admissions involving dysglycemia during the preceding two years, the number of hospitalizations for any reason during the preceding year, and the number of days during the previous year on which there was a visit to an endocrinologist, internist, or family physician. The authors also adjusted for recent prescriptions (within the preceding 180 days) for insulin, oral hypoglycemic agents, or other drugs that might influence glycemic control. Because the pharmacokinetics of sulfonylurea hypoglycemic agents can be influenced by drugs that modulate the activity of cytochrome P-450 isoenzyme 2C937, they adjusted for the receipt of commonly used inhibitors and inducers of this enzyme. Finally, they adjusted for socioeconomic status and for the number of drugs received during the previous year.

As compared with macrolide antibiotics (e.g., azithromycin), gatifloxacin was associated with an increased odds of hypoglycemia (adjusted odds ratio, 4.3; 95 percent confidence

[iii] Because any serious infection could be associated with alterations in blood glucose levels, they used patients treated with macrolide antibiotics as the control group in all analyses. Macrolides, cephalosporins, and certain fluoroquinolones are prescribed for similar community-acquired infections, but macrolides do not directly affect glucose homeostasis. Each case patient was matched to five controls.

interval, 2.9 to 6.3) and hyperglycemia (adjusted odds ratio, 16.7; 95 percent confidence interval, 10.4 to 26.8). In non-diabetics, as
compared with macrolide antibiotics, gatifloxacin was associated with increased odds of hypoglycemia (adjusted odds ratio, 9.0; 95 percent confidence interval, 1.3–63.4) and hyperglycemia (adjusted odds ratio, 12.8; 95 percent confidence interval, 5.9–27.8). All of these results were statistically significant.

The authors also observed a statistically significant but weaker association between hypoglycemia and levofloxacin (adjusted odds ratio, 1.5; 95 percent confidence interval, 1.2 to 2.0) but no increased odds of hypoglycemia after treatment with either moxifloxacin or ciprofloxacin. However, aside from gatifloxacin, there were no statistically significant differences in odds of hyperglycemia for any of the study drugs (compared to macrolides). These findings strongly support the case for gatifloxacin being uniquely associated with high rates of dysglycemic events (in diabetic and non-diabetic patients) compared to other fluoroquinolones, macrolides, and cephalosporins

Table 5. Park–Wyllie, et al: Association between Dysglycemia-Related Hospital Visits and Recent Antibiotic Use

Drug	Hypoglycemia: Adjusted OR (95% CI)			Hyperglycemia: Adjusted OR (95% CI)		
	All Patients	Diabetics	Non-Diabetics	All Patients	Diabetics	Non-Diabetics
Gatifloxacin	**4.3 (2.9-6.3)**	**4.2 (2.8–6.3)**	**9.0 (1.3–63.4)**	**16.7 (10.4–26.8)**	**23.6 (12.4–44.6)**	**12.8 (5.9–27.8)**
Levofloxacin	1.5 (1.2–2.0)	1.5 (1.2–2.0)	2.1 (0.7–6.0)	1.3 (0.9–1.9)	1.6 (1.0–2.5)	1.0 (0.5–1.8)
Moxifloxacin	0.8 (0.5–1.3)	0.8 (0.5–1.3)	1.7 (0.2–11.8)	1.7 (1.0–3.0)	1.7 (0.8–3.9)	1.6 (0.7–3.9)
Ciprofloxacin	0.9 (0.8–1.1)	0.9 (0.7–1.1)	1.2 (0.5–2.9)	1.1 (0.9–1.5)	1.3 (0.9–1.8)	0.9 (0.6–1.6)
Cephalosporins	0.9 (0.6–1.2)	0.8 (0.6–1.1)	2.3 (0.8–6.7)	1.2 (0.8–1.7)	1.0 (0.6–1.7)	1.5 (0.8–2.7)
Macrolides	1.0	1.0	1.0	1.0	1.0	1.0

Nested case-control studies (NCCs) are considered Level 2 evidence (like cohort studies). This is because unlike regular case-control studies that start with cases and look at exposure retrospectively, NCCs initially follow a cohort prospectively before designating cases and looking at exposure retrospectively (exposure in this case is ingestion of the drug). NCCs may also have less potential for bias than cohort studies, which often have difficulty with patients being lost to follow up.

The NCC by Mohr et al evaluated patients for all dysglycemic events (hypo- and hyperglycemia), while the study by Graumlich et al evaluated only hypoglycemic events.[30] The Mohr study did not find a statistically significant difference in rates of dysglycemia between gatifloxacin and levofloxacin; however, as the studies by Frothingham and Park-Wyllie have shown, levofloxacin is associated with an increased risk of hypoglycemia, while smaller than that of gatifloxacin. It is also important to note that in this study, the extent of follow up was 72 hours, but gatifloxacin does not usually cause hyperglycemia until after that time. It is stated clearly in the Tequin package insert that increases in fasting serum glucose occur "usually after the third day of Tequin administration." [31] Therefore,

one might not expect to see a large difference in dysglycemic events between gatifloxacin and levofloxacin at 72 hours follow-up because (1) both drugs are associated with initial hypoglycemia and (2) gatifloxacin-associated hyperglycemia would not necessarily be detected because the duration of follow up was insufficient. If the follow up in Mohr's study had been extended, a statistically significant difference in the rates of dysglycemic events probably would have been seen. In Graumlich's study with 12 month follow up, a statistically significant difference in the rates of hypoglycemia was seen between gatifloxacin and levofloxacin.

The Park -Wyllie study consisted of two separate NCCs to evaluate odds of gatifloxacin-associated hyper- and hypoglycemia. The follow up was as 30 days, which is long enough to detect the hyperglycemic effects of gatifloxacin. As one can see from Table 5, all of the increased odds of gatifloxacin-associated hyper- and hypoglycemia were statistically significant.

Case Reports. There are 25 case reports in the literature that describe gatifloxacin-associated dysglycemic events. [32,33,34,35,36,37,38,39,40,41,42,43,44,45,46] These reports generally describe severe or unexpected dysglycemic events, including in non-diabetic patients. Table 6 on the following page describes these events.

Table 6. Case Reports of Gatifloxacin-Associated Dysglycemia						
First Author	**Year**	**Age**	**Hyper/ Hypo [a]**	**Diabetes (Y/N)**	**Serum Glucose (mg/dl) [b]**	**Outcome**
Baker	2002	73	Hypo	Y	16	Tachycardia, diaphoresis, agitation
Biggs	2003	82	Hypo	Y	50	Mental status changes
Biggs	2003	68	Hypo	Y	70	Hypoglycemia
Biggs	2003	82	Hyper	Y	>500	Hyperglycemia
Biggs	2003	91	Hyper	N	>1000	Hyperosmolar non-ketosis
Khovidhunkit	2004	87	Hypo	Y	40	Hypoglycemia
Khovidhunkit	2004	69	Hyper	N	445	Hyperglycemia
LeBlanc	2004	84	Hypo	Y	28	Hypoglycemia
LeBlanc	2004	79	Hypo	Y	18	Coma (reversible)
Menzies	2002	74	Hypo	Y	27	Tonic-clonic seizure
Menzies	2002	94	Hypo	Y	33	Hypoglycemia
Menzies	2002	71	Hypo	Y	22	Tachycardia, diaphoresis, agitation
Arce	2004	46	Hyper	N	500	Hyperglycemia
Arce	2004	77		N	694	Admitted w/ CHF exacerbation; day 6-hyperglycemia; day 12-death.
Bhatia	2004	N/A	Hyper	N/A	N/A	N/A
Brogan	2005	52	Hypo	Y	23	Coma (reversible)
Donaldson	2004	64	Hyper	N	607	Hyperglycemia
Blommel	2005	65	Hyper	N	1121	Hyperglycemia
Happe	2004	60	Hyper	N	942	Hyperosmolar non-ketosis
Happe	2004	47	Hyper	N	1456	Hyperosmolar non-ketosis
Bhasin	2005	89	Hypo	Y	34	Coma (reversible)
Bhasin	2005	80	Hypo	N	39	Hypoglycemia
Bhasin	2005	58	Hypo	Y	42	Hypoglycemia
Beste	2005	71	Hyper	N	553	Hyperglycemia
Stading	2005	57	Hyper	N	992	Blurry vision, polyuria, thirst

a: hyperglycemia or hypoglycemia
b: highest or lowest glucose recorded in case description
c: death, mental status changes, hyperosmolar non-ketosis, coma, seizure

Summary of Table 6 Data	
Variable	**No. (%)**
Diabetes present	13/24 (54%)
Hyperglycemia	11/24 (46%)
Hypoglycemia	13/24 (54%)
Serious Outcome [c]	9/24 (38%)

It is important to note that 46% of the patients were non-diabetic and 38% of patients had a serious outcome.

Animal Studies/In-Vitro Analyses

There are few medications that cause opposing physiologic effects; however, there is a sound scientific explanation for why gatifloxacin seems to cause both hyper- and hypoglycemia. Studies in in-vitro culture of murine pancreatic β-cells have shown that gatifloxacin inhibits pancreatic β-cell Potassium $(K)_{ATP}$ channels causing increased insulin secretion and hypoglycemia.[47 48] Conversely, manufacturer-sponsored animal studies have also shown that gatifloxacin caused vacuolation of the insulin-containing β-cells, causing decreased insulin secretion and hyperglycemia.[49] A recent animal study by Ishiwata et al showed that gatifloxacin-mediated epinephrine release may be responsible for hyperglycemia seen at higher doses.[50] There is no way of predicting which effect will predominate; however, hypoglycemia tends to occur prior (within hours after initial dose) [51]

[52] to hyperglycemia (within days after initial dose).[53] It is unclear exactly when vacuolation of pancreatic β-cells occurs because most of the pre-approval animal studies evaluated histologic specimens that were prepared after 1 month of daily gatifloxacin dosing. However, this mechanism of early hypoglycemia and later hyperglycemia has biologic plausibility given that receptor blockade generally occurs immediately after drug reaches target tissue, whereas vacuolation requires intracellular ultrastructural changes and may take longer [i.e. days] to occur.

Gatifloxacin and Dysglycemia in Non-Diabetics: Review of the Evidence

Given the mechanisms for gatifloxacin-associated dysglycemia, it is biologically plausible that non-diabetics should be affected as well as diabetics, and the evidence supports this conclusion.

- The FDA medical officer reviewing the pre-approval trial AI420-036 in non-diabetics reported that "There was a transient decrease in serum glucose at all dose levels [of gatifloxacin] at the one hour time point on Day 1 with a prompt recovery by the end of the second hour."
- 10/24 (46%) case reports of gatifloxacin-associated dysglycemia involved non-diabetic patients.
- The TeqCES Phase IV study in 15,000 patients showed that of non-diabetics who took gatifloxacin, 0.007% (70 per million patients) had hyperglycemic events and 0.03% (300 per million) had hypoglycemic events. [54]
- The 2006 study by Park-Wyllie showed that non-diabetic patients receiving gatifloxacin had approximately 13 times the odds of having a hyperglycemic episode and 9 times the odds of having a hypoglycemic episode compared to those taking macrolide antibiotics (e.g. erythromycin).[55] Both of these results were statistically significant.

It can be seen from these data that in non-diabetics, the absolute risk of gatifloxacin-associated dysglycemia is relatively low, but the odds ratio (compared to macrolides) is extremely high. Even if the absolute risk is low, there are multiple fluoroquinolones and/or antibiotics with similar indications that are safer than gatifloxacin.

Evidence Summary

Based on Public Citizen's analysis (Table 1, p. 2) and the other data cited above, it is clear that the rates of gatifloxacin-associated dysglycemia AERs are significantly higher than those for the comparator drugs (levofloxacin, moxifloxacin, ciprofloxacin, and azithromycin). The same is true for rates of gatifloxacin-associated dysglycemia AERs with death. This analysis is consistent with results from animal studies, in-vitro analyses, human volunteer studies, case reports, cohort/case-control studies, and clinical trials. The 2002 TeqCES study in 15,000 patients offers compelling evidence for gatifloxacin conferring increased risk for dysglycemia in all patients (including non-diabetics). Similarly, the 2006 nested case-control study by Park-Wyllie et al offers persuasive evidence for gatifloxacin causing increased odds of dysglycemic events in all patients (including non-diabetics).

Regulatory Background

Evidence that gatifloxacin may adversely affect pancreatic function, insulin production/distribution, and/or glucose homeostasis was initially documented in the drug's NDA approval documents in December of 1999. In manufacturer-sponsored animal studies, gatifloxacin caused ultrastructural changes in pancreatic islets and caused insulin/glucose abnormalities (see Animal Studies/In-Vitro Analyses section).[56] Subsequent pre-approval, human volunteer studies also showed evidence of gatifloxacin-associated changes in serum insulin and glucose levels.[57] Based on the pre-approval data summarized previously, the Tequin label approved in 1999 (see Table 7 below) included the following general PRECAUTION: "As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic (e.g., glyburide) or with insulin. In these patients, the monitoring of blood glucose is recommended." [58] Table 7 summarizes the various relabelings and other regulatory actions in the US, Canada, and Japan. The label changes in the US in 2001 and 2002 did not significantly change rates of dysglycemia AERs per million prescriptions (see Figure 1).

Table 7. Timeline: Regulatory Background of Gatifloxacin in the US, Canada, and Japan*

US	DA		LR	LR		LR		LRC
Canada			DA	LR				PHA
Japan				DA	LRC			
Year	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**

*DA=drug approved
LR=label revision due to gatifloxacin-associated dysglycemia
LRC=label revision featuring a CONTRAINDICATION in diabetic patients
PHA=public health advisory for diabetics not to use gatifloxacin

Shortly after gatifloxacin's approval in the US in December 1999, the FDA began to receive gatifloxacin AERs listing either hypo- or hyperglycemia as the primary term.[59,60] Furthermore, case reports of gatifloxacin-associated dysglycemia began to be published in the medical literature (see Table 6). This led to the label revision of August 2001 which offered stronger, more prominent language describing gatifloxacin-associated dysglycemia risk in diabetics. In the Special Populations section: "careful monitoring of blood glucose is recommended when Tequin is administered to diabetic patients receiving treatment with oral hypoglycemic agents with or without insulin." [61]

As data (case reports, AERs) accumulated, a second manufacturer-sponsored, post-marketing study (the first was the TeqCES study) was performed in 70 healthy, diabetic Americans (see Table 2), and the results confirmed that gatifloxacin was associated with glucose homeostasis abnormalities.[62] This resulted in the label change in the US in October 2002 to include a WARNING describing potential gatifloxacin-associated dysglycemia in diabetics. Furthermore, it warned that "elderly patients who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems and/or are

taking concomitant medications associated with hyperglycemia may be at particular risk of serious hyperglycemia." [63] The label was again changed in January 2004 to include "hypoglycemic coma" in the ADVERSE REACTIONS section.[64]

In February 2006, the Tequin Package Insert (distributed in the US) was updated for a fourth time to include a CONTRAINDICATION in diabetic patients due to serious reports of dysglycemia; the WARNINGS and PRECAUTIONS sections were updated to identify other risk factors for dysglycemia including older age, renal insufficiency, and use of concomitant glucose-altering medications. This label revision was *not* included in a "black box," which is the FDA's strongest labeling requirement for high-risk medicines.[65] The BMS "Dear Doctor" released in the US on February 16, 2006 stated that "In postmarketing experience worldwide, serious cases of both hypoglycemia and hyperglycemia have been reported in patients receiving Tequin. Although most of these cases were reversible, very rare events of dysglycemia were life-threatening, and a few resulted in fatal outcomes." [66]

A similar situation unfolded in Canada where the drug was approved in February of 2001. In 2003, Health Canada's CADRMP revealed that hypo- and hyperglycemia had "been reported more frequently with gatifloxacin than with other quinolone antibiotics." [67] Furthermore, as discussed above, the 2002 TeqCES study in 15,000 patients showed a high proportion of gatifloxacin-associated dysglycemic events in both diabetic and non-diabetic patients. Based on this study, the manufacturer reported, "Disturbances of blood glucose, including symptomatic hyper-and hypoglycemia, have been reported with Tequin, usually but not always in diabetic patients." [68] In December 2002, BMS-Canada made a label revision to include a PRECAUTION for use in diabetic patients and those with decreased renal function, elderly patients, and those with underlying medical problems.[69] (The Japan package insert was changed in March of 2003 to include a CONTRAINDICATION in diabetic patients).[70] In the UK, the drug is not available.[71]

In December 2005, BMS-Canada distributed a "Dear Doctor" letter reminding Canadian physicians of the WARNING on the label regarding gatifloxacin-associated dysglycemia.[72] In February 2006, Health Canada advised diabetic patients, as a precaution, not to use gatifloxacin due to concerns about glucose homeostasis abnormalities. (This advice was based on recommendations submitted to the department by the manufacturer).[73] Unlike in the US, the Canadian label has not been changed to list gatifloxacin as being contraindicated in diabetics.

Gatifloxacin's FDA Labeling Revisions Proven Ineffective

It can be seen from Figure 1 that the 3 label changes in 2001, 2002, and 2004 have not substantially decreased the rate of gatifloxacin-associated dysglycemia AERs. There are 2 probable reasons for this: (1) evidence suggests that label revision is usually insufficient to satisfactorily change physician prescribing practices, and (2) the label revisions of the US Tequin package insert have identified only diabetic patients as having high risk for gatifloxacin-associated dysglycemia; therefore, non-diabetic patients at increased risk for the same would continue to be prescribed this drug.

A 2002 study by the FDA measured adherence to various black box labeling

recommendations. The study used a large health care company's administrative claims database, which included 1,308 patients who were newly prescribed pemoline from January 1998 to March 2000. While the recommendation that pemoline be used only as second-line therapy for ADHD had been in place since the 1996 label, only 237 patients (34%) were found to have received another ADHD drug prior to pemoline. Dividing the data into two six-month periods, before and after the June 1999 labeling change, the authors found that the new label had no measurable effect on liver enzyme testing rates (the pemoline label recommended that patients have periodic liver enzyme testing). Twelve percent of pre-label change patients received baseline liver enzyme tests, compared to 11% of patients after the labeling change. The percentage of patients receiving any follow-up liver enzyme tests (the label recommended biweekly testing) was similarly low before and after the labeling change (9% pre-change vs. 12% post-change). This study showed that labeling changes, including black-box warnings, had no measurable effect on compliance with the labeling recommendations for pemoline.[74]

A 2000 study by Smalley, et al sought to evaluate the impact of the FDA's 1998 regulatory action regarding cisapride. In June 1998, the FDA determined that use of cisapride was contraindicated in patients with prolonged QT syndrome and informed practitioners through additions to the boxed warning in the label and a "Dear Doctor" letter sent by the drug's manufacturer. In the year prior to regulatory action, cisapride use was contraindicated for 26%, 30%, and 60% of users at study sites A, B, and C, respectively. In the year after regulatory action, use was contraindicated for 24%, 28%, and 58% of users, a reduction in contraindicated use of approximately 2 per 100 cisapride users at each site. When the analysis was restricted to new users of cisapride again, only minor reductions in contraindicated use were found. The authors concluded that the FDA's 1998 regulatory action regarding cisapride use "had no material effect on contraindicated cisapride use." [75]

Another study in 2006 by Lasser, et al sought to determine how frequently clinicians prescribe drugs in violation of black box warnings and to determine how frequently such prescribing results in harm. Of 324,548 patients (at 51 outpatient practices) who received a medication in 2002, 2354 (0.7%) received a prescription in violation of a black box warning. The number of medications taken, older age, the number of medical problems, and certain sites of care were associated with violations. Less than 1% of patients who received a drug in violation of a black box warning had an adverse drug event as a result. Of 30,605 patients prescribed a drug with a drug-disease black box WARNING, 209 (0.7%) had a contraindicated disease.[76]

Increased Risk without Unique Benefit

The complete list of fluoroquinolones (along with their indications) currently approved by the FDA is listed in Table 8 on page 12. It can be seen that there are many other drugs in this class that have the same approved indications as gatifloxacin (see Table 7 below). Each condition for which gatifloxacin is indicated has one or more FDA-approved quinolones that could be used instead. Of course, there are drugs in other antibiotic classes approved for most or all of these indications as well.

Table 8. FDA Approved Fluoroquinolone Indications																											
Drug	Adults																									Ped	
	Acute maxillary sinusitis	Acute CPOD exacerbation	Nosocomial pneumonia	Community-acquired pneumonia (CAP)	CAP with action against MDRSP	Gram (-) pneumonia	Complicated skin/skin structure infections	Uncomplicated skin/skin structure infections	Bone and joint infections	Acute bacterial prostatitis	Chronic bacterial prostatitis	Complicated Urinary Tract Infection	Uncomplicated Urinary Tract Infection	Acute pyelonephritis	Complicated intra-abdominal infections	Infectious diarrhea	Typhoid fever	Inhalation anthrax	Non-gonococcal urethritis/cervicits	Uncompliacted cerival/urethral gonorrhea	Mixed infections of the urethra/cervix	Transrectal prostate biopsy prophylaxis	Acute pelvic inflammatory disease	Pharyngitis	Complicated urinary tract infections	Pyelonephritis
Gatifloxacin	**x**	**x**		**x**	**x**			**x**				**x**	**x**	**x**						**x**						
Ciprofloxacin	x					x	x	x	x		x	x	x	x	x	x	x	x		x					x	x
Lomefloxacin		x										x	x									x				
Norfloxacin										x	x	x	x							x						
Ofloxacin		x		x				x		x		x	x						x	x	x		x			
Levofloxacin	x	x	x	x	x		x	x			x	x	x	x												
Gemifloxacin		x		x	x																					
Moxifloxacin	x	x	x																							

Fluoroquinolone Class Effects. The quinolone class of drugs possesses a risk profile that includes, in addition to hypoglycemia, cardiac toxicity, central nervous system (CNS) toxicity, liver toxicity, hemolytic uremic syndrome (HUS), joint disorder and/or tendon rupture (JD), and anaphylaxis. Consequently, the FDA requested that the manufacturer evaluate their entire study population from the pre-approval trials for these effects. Table 9 below outlines the FDA Medical Officer's comments from the Tequin NDA Approval Documents regarding these effects. It can be seen that, aside from possibly a small decreased risk of JD with gatifloxacin, this drug had the same or worse risk of all of these class-specific side effects.[77]

Table 9. FDA Medical Officer Analysis of Tequin Safety and Phase II/III Studies to Evaluate the Degree of Gatifloxacin's Class-Specific Side Effects Compared to other Quinolones		
Reaction	**Is Gatifloxacin Better, Worse, or the Same?**	**FDA MO Summary**
Photo-toxicity	Same	A complex analysis "failed to identify any difference between gatifloxacin-treated patients and those who received other quinolones (ciprofloxacin, levofloxacin, or ofloxacin) or other antibiotics (cephalosporins or macrolides)."
Cardiac Toxicity	Same	"The evaluation of the Phase III clinical adverse event database related to the cardiovascular system in over 8,500 patients treated with gatifloxacin failed to reveal any striking differences between gatifloxacin and comparator."
CNS Toxicity	Worse	"There were 5 patients reported to have had convulsions in the database. One patient was treated with ciprofloxacin and 4 patients were treated with gatifloxacin. None of these cases were felt to be related to study drug by the site investigators."
Liver Toxicity	Same	"there is no serious or significant hepatotoxicity in the gatifloxacin treated patient group (3,043 patients). In addition, liver test abnormalities were seen at a rate and level comparable to the 'comparator' drugs."
HUS	Same	No cases of HUS were reported in patients receiving either gatifloxacin or comparator drugs.
Joint Disorder	Better	"Overall, the incidence of these events was lower among gatifloxacin-treated patients (<0.1%) compared to those treated with quinolones or non-quinolone antibiotics (0.3% in each)." [iv]
Anaphy-laxis	Worse	"There were 13 cases of "allergic reaction" which was further classified as urticaria, hives, or drug reaction. Nine of these were in the gatifloxacin group and 4 were in the comparator group (1 patient given clarithromycin; 3 patients given ciprofloxacin."

Rezulin: What not to Do. This section outlines the needless morbidity and mortality that can result from failure to ban a drug (troglitazone [Rezulin], a diabetes drug) in the face of post-approval evidence that risks clearly outweigh benefits.[78]

- March 1997: U.S. Rezulin marketing begins
- April 1997: **Label revision**
- November 1997: **Label revision**
- Dec 1997: Drug is withdrawn in the UK after 130 cases of liver damage occur (including 6 deaths); **label revision**
- July 1998: Public Citizen's Health Research Group petitions FDA to ban Rezulin after 560 cases of liver damage, including 26 deaths; **label revision**

[iv] There is no evidence in the medical literature that there are any differences in the rates of joint disorders and/or tendon rupture among the fluoroquinolones. The 2004 Tequin package insert states "Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. Tendon rupture can occur during or after therapy with quinolones."

- March 1999: FDA advisory committee meets to discuss Rezulin-associated liver toxicity; at this point, there are 43 deaths from Rezulin-associated liver failure
- June 1999: **Label revision**
- Early 2000: Some FDA physicians state that the drug should be banned
- March 2000: Rezulin is withdrawn in the US; by then, 63 liver deaths, seven liver transplants

Clearly, Rezulin should have been banned in the US much earlier than it was. Furthermore, it can be seen that the 5 label revisions did not decrease number of cases of Rezulin-associated liver toxicity or death.

Recommendations

The FDA has instructed the manufacturer to revise Tequin's label to include a CONTRAINDICATION for use in diabetic patients. However, Public Citizen believes there are 6 primary reasons why gatifloxacin should be banned such that even product currently in the chain of commerce is not sold: (1) there is strong evidence to support the existence of a causal relationship between gatifloxacin and dysglycemic events in non-diabetics (2) the rates of gatifloxacin-associated dysglycemia AERs per million prescriptions are 11-12 times greater than the comparator drug with the second highest adverse event rates (moxifloxacin in the analyses by Public Citizen and Frothingham, et al), (3) the rates of gatifloxacin-associated dysglycemia AERs *with the outcome of death* per million prescriptions are 16-18 times greater than comparator drugs with the second highest rates (moxifloxacin and levofloxacin in the analyses by Public Citizen and Frothingham et al, respectively), (4) "Dear Doctor" letters and label changes often do not adequately change physician prescribing practices, (5) gatifloxacin has no FDA-approved indication that other antibiotics (quinolones or other antibiotics with the same indications) do not also have, and (6) compared to other fluoroquinolones, gatifloxacin does not offer a confirmed decreased risk of any class-specific side effect.

The manufacturer admits that the drug has been known to cause dysglycemic events, resulting in label changes in the US, Canada, and Japan. The Tequin Package Insert has been revised 4 times since its approval in the US because of the drug's association with dysglycemic effects.[79] As our investigation has shown, not only does this drug cause glucose homeostasis abnormalities, the rates of dysglycemia adverse events with fatal outcome are much higher than for other drugs in the same class or with similar indications. In Table 9, even though the manufacturer reported that gatifloxacin had fewer adverse events involving joint disorder and/or tendon rupture, there is no evidence in the medical literature to support this conclusion; therefore, this should not be used as a reason to allow this drug to remain on the market. For non-diabetics, the absolute risk of gatifloxacin-associated dysglycemia is lower, but the odds ratio (compared to macrolides) is extremely high (13 times the odds of having a hyperglycemic episode and 9 times the odds of having a hypoglycemic episode). Even if the absolute risk is low, given the fact that there are multiple fluoroquinolones and/or antibiotics with similar indications that are safer than gatifloxacin, the FDA should ban this drug. Banning gatifloxacin will force clinicians to

choose safer alternative fluoroquinolones or other antibiotics and will prevent product currently in the chain of commerce from unnecessarily injuring additional patients.

Environmental Impact Statement

Nothing requested in this petition will have an impact on the environment.

Certification

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

We look forward to a prompt response to this petition.

Sincerely,

Joseph Baker, MD, MPH
Research Analyst

Sidney Wolfe, MD
Director

Peter Lurie, MD, MPH
Deputy Director

Public Citizen's Health Research Group

Table 10. Oxford Centre for Evidenced Based Medicine, Levels of Evidence[13]				
1	**2**	**3**	**4**	**5**
a. SR (with homogeneity) of RCT b. Individual RCT (with narrow Confidence Interval) c. "All or None" criteria[13]	a. SR (with homogeneity) of cohort studies b. Individual cohort study (including low quality RCT); c. "Outcomes" Research; Ecological studies	SR (with homogeneity) of case-control studies b. Individual Case-Control Study	Case-series (and poor quality cohort and case-control studies)	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
SR=Systematic Review, RCT=Randomized Controlled Trial				

[1] Food and Drug Administration. Temafloxacin P92-16. 1998. (Accessed March 27, 2006, at http://www.fda.gov/bbs/topics/NEWS/NEW00279.html).

[2] Rubinstein E. History of quinolones and their side effects. Chemotherapy 2001;47:Suppl 3:3-8, 44 8.

[3] Rubinstein E. History of quinolones and their side effects. Chemotherapy 2001;47:Suppl 3:3-8, 44 8.

[4] Food and Drug Administration. Glaxo Wellcome voluntarily withdraws Raxar (grepafloxacin). 1999. (Accessed March 26, 2006, at http://www.fda.gov/medwatch/SAFETY/1999/raxar.html).

[5] Ball P. New antibiotics for community-acquired lower respiratory tract infections: improved activity at a cost? Int J Antimicrob Agents 2000;16:263-72.

[6] Ball P. New antibiotics for community-acquired lower respiratory tract infections: improved activity at a cost? Int J Antimicrob Agents 2000;16:263-72.

[7] Center for Drug Evaluation and Research, Office of Drug Safety. Questions and answers on trovafloxacin: public health advisory. August 2003. (Accessed February March 26, 2006, at http://www.fda.gov/cder/news/ trovan/qa.htm).

[8] Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dresser L, Low DE, Mamdani MM. Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults. N Engl J Med. 2006 Mar 1.

[9] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 3, 2006, at (http://www.fda.gov/cder/foi/nda/99/21061_Tequin_medr_P1.pdf).

[10] Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. Clin Infect Dis 2005;41:1269-76.

[11] Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. Clin Infect Dis 2005;41:1269-76.

[12] Létourneau G, Morrison H, McMorran M. Gatifloxacin: hypoglycemia and hyperglycemia. Can. Adverse React Newsl. 2003;13(3):1-2.

[13] Oxford Centre for Evidenced Based Medicine. (Assessed April 26, 2006 from http://www.cebm.net/levels_of_evidence.asp#notes).

[14] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 3, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_medr_P14.pdf).

[15] Tequin (gatifloxacin) [package insert]. Princeton, NJ: Bristol-Myers Squibb, 2004.

[16] Tequin (gatifloxacin) [package insert]. Princeton, NJ: Bristol-Myers Squibb, 2004.

[17] Gajjar DA, LaCreta FP, Kollia GD, et al. Effect of multiple-dose gatifloxacin or ciprofloxacin on glucose homeostasis and insulin production in patients with noninsulin-dependent diabetes mellitus maintained with diet and exercise. Pharmacotherapy 2000;20:76S–86S.

[18] Correa JC, Badaro R, Bumroongkit C, et al. Randomized, open-label, parallel-group, multicenter study of the efficacy and tolerability of IV gatifloxacin with the option for oral stepdown gatifloxacin versus IV ceftriaxone (with or without erythromycin or clarithromycin) with the option for oral stepdown clarithromycin for treatment of patients with mild to moderate community-acquired pneumonia requiring hospitalization.
Clin Ther 2003; 25:1453–68.

[19] Mendonca JS, Yamaguti A, Correa JC, Badaro R. Gatifloxacin in the treatment of community-acquired pneumonias: a comparative trial of ceftriaxone, with or without macrolides, in hospitalized adult patients with mild to moderately severe pneumonia. Braz J Infect Dis 2004; 8: 90–100.

[20] Cannon CP, Braunwald E, McCabe CH, et al. Antibiotic treatment of *Chlamydia pneumoniae* after acute coronary syndrome. N Engl J Med 2005; 352:1646–54.

[21] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 3, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_medr_P14.pdf).

[22] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 12, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_medr_P1.pdf and http://www.fda.gov/cder/foi/nda/99/21061_Tequin_medr_P14.pdf).

[23] Bristol-Myers Squibb Company. (Accessed March 17, 2006, at http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/09-20-2000/0001317865&EDATE=).

[24] *Tequin*™, gatifloxacin tablets [product monograph]. Montreal: Bristol-Myers Squibb Canada Inc.; 2002 Dec 24.

[25] The Food and Drug Administration. The Clinical Impact of Adverse Event Reporting. (Accessed March 5, 2006 at http://www.fda.gov/medwatch/articles/medcont/postrep.htm)

[26] Greenberg AL, Decerbo M, Fan J. Gatifloxacin therapy associated with hypoglycemia. Clin Infect Dis 2005;40:1210-1.

[27] Mohr JF, McKinnon PS, Peymann PJ, Kenton I, Septimus E, Okhuysen PC. A retrospective, comparative evaluation of dysglycemias in hospitalized patients receiving gatifloxacin, levofloxacin, ciprofloxacin, or ceftriaxone. Pharmacotherapy 2005;25: 1303-9.

[28] Lomaestro BM, Lodise TP. Comparison of glucose intolerance between gatifloxacin and piperacillin-tazobactam in elderly, hospitalized patients [abstract A-1093]. In: Program and abstracts of the 44th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). Washington, DC: American Society for Microbiology, 2004:19.

[29] Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dresser L, Low DE, Mamdani MM. Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults. N Engl J Med. 2006 Mar 1.

[30] Graumlich JF, Habis S, Avelino RR, Salverson SM, Gaddamanugu M, Jamma K, Aldag JC. Hypoglycemia in inpatients after gatifloxacin or levofloxacin therapy: nested case-control study. Pharmacotherapy. 2005 Oct;25(10):1291-5.

[31] Tequin (gatifloxacin) [package insert]. Princeton, NJ: Bristol-Myers Squibb, 2004.

[32] Baker SE, Hangii MC. Possible gatifloxacin-induced hypoglycemia. Ann Pharmacother 2002;36:1722-6.

[33] Biggs WS. Hypoglycemia and hyperglycemia associated with gatifloxacin use in elderly patients. J Am Board Fam Pract 2003;16:455-7.

[34] Khovidhunkit W, Sunthornyothin S. Hypoglycemia, hyperglycemia, and gatifloxacin. Ann Intern Med 2004;141:969.

[35] LeBlanc M, Belanger C, Cossette P. Severe and resistant hypoglycemia associated with concomitant gatifloxacin and glyburide therapy. Pharmacotherapy 2004; 24:926-31.

[36] Menzies DJ, Dorsainvil PA, Cunha BA, Johnson DH. Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. Am J Med 2002;113:232-4.

[37] Arce FC, Bhasin RS, Pasmantier R. Severe hyperglycemia during gatifloxacin therapy in patients without diabetes. Endocr Pract 2004;10:40-4.

[38] Bhatia V, Bhatia R, Dhindsa S. Gatifloxacin- induced hyperglycemia. Endocr Pract 2004;10:86.

[39] Brogan SE, Cahalan MK. Gatifloxacin as a possible cause of serious postoperative hypoglycemia. Anesth Analg 2005;101: 635-6. [Erratum, Anesth Analg 2005;101: 1614.]

[40] Donaldson AR, Vandiver JR, Finch CK. Possible gatifloxacin-induced hyperglycemia. Ann Pharmacother 2004;38:602-5.

[41] Blommel AL, Lutes RA. Severe hyperglycemia during renally adjusted gatifloxacin therapy. Ann Pharmacother. 2005 Jul-Aug;39(7-8):1349-52. Epub 2005 Jun 7.

[42] Happe MR, Mulhall BP, Maydonovitch CL, Holtzmuller KC. Gatifloxacin-induced hyperglycemia. Ann Intern Med 2004;141: 968-9.

[43] Bhasin, Romi MD, PhD; Arce, Francis Clifford MD; Pasmantier, RoseMarie MD Hypoglycemia Associated with the Use of Gatifloxacin. American Journal of the Medical Sciences. 330(5):250-253, November 2005.

[44] Létourneau G, Morrison H, McMorran M. Gatifloxacin: hypoglycemia and hyperglycemia. Can. Adverse React Newsl. 2003;13(3):1-2.

[45] Beste LA, Mersfelder TL. Hyperglycemia and gatifloxacin: a case report and summary of current literature. Am J Geriatr Pharmacother. 2005 Dec;3(4):262-5.

[46] Stading JA, Chock AW, Skrabal MZ, Faulkner MA. Development of diabetes after gatifloxacin therapy. Am J Health Syst Pharm. 2005 Nov 1;62(21):2293-5.

[47] Saraya A, Yokokura M, Gonoi T, Seino S. Effects of fluoroquinolones on insulin secretion and beta-cell ATP-sensitive K+ channels. Eur J Pharmacol 2004;497:111-7.

[48] Maeda N, Tamagawa T, Niki I, et al. Increase in insulin release from rat pancreatic islets by quinolone antibiotics. Br J Pharmacol 1996;117:372-6.

[49] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 3, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_pharmr_P2.pdf).

[50] Létourneau G, Morrison H, McMorran M. Gatifloxacin: hypoglycemia and hyperglycemia. Can. Adverse React Newsl. 2003;13(3):1-2.

[51] Tequin (gatifloxacin). Princeton, N.J.: Bristol-Myers Squibb, 2004 (package insert).

[52] Saraya A, Yokokura M, Gonoi T, Seino S. Effects of fluoroquinolones on insulin secretion and beta-cell ATP-sensitive K+ channels. Eur J Pharmacol 2004;497:111-7.

[53] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 3, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_pharmr_P2.pdf).

[54] *Tequin*™, gatifloxacin tablets [product monograph]. Montreal: Bristol-Myers Squibb Canada Inc.; 2002 Dec 24.

[55] Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dresser L, Low DE, Mamdani MM. Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults. N Engl J Med. 2006 Mar 1.

[56]Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 12, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_pharmr_P2.pdf)

[57] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 12, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_medr_P1.pdf)

[58] Tequin (gatifloxacin). Princeton, N.J.: Bristol-Myers Squibb, 1999 (package insert).

[59] Food and Drug Administration. Adverse Event Reporting System Database 2000-2005.

[60] Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. Clin Infect Dis 2005;41:1269-76.

[61] Tequin (gatifloxacin). Princeton, N.J.: Bristol-Myers Squibb, 2001 (package insert).

[62] Tequin (gatifloxacin). Princeton, N.J.: Bristol-Myers Squibb, 2002 (package insert).

[63] Tequin (gatifloxacin). Princeton, N.J.: Bristol-Myers Squibb, 2002 (package insert).

[64] Tequin (gatifloxacin). Princeton, N.J.: Bristol-Myers Squibb, 2004 (package insert).

[65] Bristol-Myers-Squibb. Dear Doctor Letter: Gatifloxacin. February 15, 2006.

[66] Bristol-Myers-Squibb. Dear Doctor Letter: Gatifloxacin. February 15, 2006.

[67] Létourneau G, Morrison H, McMorran M. Gatifloxacin: hypoglycemia and hyperglycemia. Can. Adverse React Newsl. 2003;13(3):1-2.

[68] *Tequin*™, gatifloxacin tablets [product monograph]. Montreal: Bristol-Myers Squibb Canada Inc.; 2002 Dec 24.

[69] *Tequin*™, gatifloxacin tablets [product monograph]. Montreal: Bristol-Myers Squibb Canada Inc.; 2002 Dec 24.

[70]Japan Ministry of Health, Labor and Welfare. Gatiflo Dear Doctor Letter in Japan. PJB Publication Ltd; March 10, 2003.

[71] National Electronic Library of Medicine, United Kingdom National Health Service. (Accessed March 30, 2006, at http://www.druginfozone.nhs.uk/Record%20Viewing/viewRecord.aspx?id=562977).

[72] Bristol-Myers-Squibb-Canada. Dear Doctor Letter: Gatifloxacin. December 19, 2005.

[73] Health Canada Advisory Notice re: Gatifloxacin. February 16, 2006.

[74] Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A Study of Compliance with FDA Recommendations for Pemoline (Cylert). Journal of the American Academy of Child and Adolescent Psychiatry. 2002 July;41(7):785-790.

[75] Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of Food and Drug Administration regulatory action. JAMA 2000;284:3036-9.

[76] Lasser KE, Seger DL, Yu DT, et al. Adherence to black box warnings for prescription medications in outpatients. Arch Intern Med 2006;166:338-44.

[77] Food and Drug Administration, Approval Documents for Tequin: NDA 21-061 and 21-062 (Assessed March 12, 2006, at http://www.fda.gov/cder/foi/nda/99/21061_Tequin_medr_P1.pdf)

[78] Public Citizen Health Research Group. Accessed March 15, 2006, at http://www.citizen.org/publications/release.cfm?ID=7410&secID=1666&catID=126).

[79] Center for Drug Evaluation and Research, Food and Drug Administration. (Accessed on April 1, 2006, at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/Retrieved).