CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-404

21-405

21-061/S010, S016

21-062/S011, S017

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH	ODS POSTMARKETING SAFETY REVIEW	
TO: Renata Albrecht, M.D., Acting Director Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590	**FROM:** Sarah J. Singer, R.Ph., Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430	**ODS PID#, DATE:** D020236 June 10, 2002
DESIRED COMPLETION DATE: July 2, 2002 **DATE RECEIVED BY ODS:** May 16, 2002	**REQUESTOR:** Diana Willard, Project Manager	
DRUG: Gatifloxacin (Tequin®)	**NDA #:** 21-061/SLR-016 21-062/SLR-017	**SPONSOR:** Bristol-Myers Squibb

EVENT:
Disturbances of glucose homeostasis

EXECUTIVE SUMMARY:
ODS was invited to comment on Bristol-Myers Squibb's labeling revisions regarding gatifloxacin (Tequin®)-associated disturbances of glucose homeostasis, as well as the company's educational program to communicate those changes.

In general, ODS thinks BMS's revisions are acceptable. However, we do make some recommendations for changes. ODS is especially concerned that the labeling and educational campaign need to reflect the fact that elderly patients "who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems, and/or taking concomitant medications associated with hyperglycemia" may be most at risk.

REASON FOR REQUEST/REVIEW:
Bristol-Myers Squibb has filed Changes Being Effected supplements related to gatifloxacin-associated disturbances of glucose homeostasis. Since ODS has been quite concerned about such events since shortly after the approval of Tequin® in December 1999 (an email regarding cases of hyperglycemic hyperosmolar nonketotic coma was sent to the Medical Officer for Tequin® in May 2000 and the first official document on hypo- and hyperglycemia was sent in July 2000), ODS was invited to comment on the company's labeling changes.

SEARCH DATE:	DATABASE SEARCHED:
May 17, 2002	Adverse Event Reporting System (AERS)

SEARCH CRITERIA:
Drug Name: Gatifloxacin (Tequin®) as a suspect drug
MedDRA Terms:

Search #1 (Hypoglycemia): BLOOD GLUCOSE DECREASED (Preferred Term)
HYPOGLYCAEMIC CONDITIONS NEC [A High-Level (grouping) Term]

Search #2 (Hyperglycemia): All are Preferred Terms
BLOOD GLUCOSE INCREASED
HYPERGLYCAEMIA NOS
DIABETES MELLITUS AGGRAVATED
DIABETES MELLITUS INADEQUATE CONTROL
DIABETES WITH HYPEROSMOLARITY
DIABETIC HYPEROSMOLAR COMA
DIABETIC HYPEROSMOLAR NON KETOACIDOSIS
NONKETOTIC HYPERGLYCAEMIC-HYPEROSMOLAR COMA

SEARCH RESULTS:
After merging duplicate cases, there were 110 unduplicated cases of hypoglycemia and 85 of hyperglycemia with gatifloxacin as a suspect drug in AERS on May 17, 2002. Relevant features of the cases are presented below.

	HYPOGLYCEMIA	HYPERGLYCEMIA
Unduplicated cases	**N=110**	**N=85**
Age (years)	**N=81**	**N=71**
Range	32-96	27-98
Median	72	70
Gender	**N=85**	**N=77**
Male	31	26
Female	54	51
Serious*	**N=59**	**N=39**
Death	0	5
Life-threatening	9	5
Hospitalization	50	29
Time to diagnosis (days)	**N=68**	**N=61**
Range	<1-10	<1-39
Median	1	4
Lowest (hypo-) or highest (hyper-) blood glucose (mg/dL)	**N=77**	**N=68**
Range	14-80	122-1712
Median	40	494
Baseline blood glucose (mg/dL)	**N=21****	**N=27****
Range	65-300	92.5-433
Median	124	126
History of diabetes	**N=97 (88%)**	**N=42 (49%)**
Stated to have no history of diabetes	**N=0**	**N=14**
Events	**N=33**	**N=21**
Adrenergic symptoms	20	
CNS symptoms	22	9
Weakness, fatigue		5
Thirst, polyuria		4
Hyperosmolar nonketosis		5
New-onset diabetes		4
Diabetic ketoacidosis		1

*By regulatory definition: Resulting in death or disability, considered life-threatening by the reporter, or involving initial or prolonged hospitalization.
**Additional cases (3 of hypoglycemia and 6 of hyperglycemia) stated that the patient's baseline glucose had been "well-controlled", "WNL", or "stable" without providing a specific level.

LITERATURE:
A search of PubMed for any citation on gatifloxacin and glucose, hyperglycemia, or hypoglycemia found only three articles. All are by Bristol-Myers Squibb and represent information available to the FDA at the time gatifloxacin was approved. The citations are given below.

Grasela DM. Clinical pharmacology of gatifloxacin, a new fluoroquinolone. Clin Infect Dis **2000**;31 Suppl 2:S51-8.

Gaijjar 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.

Gaijjar DA, LaCreta FP, Uderman HD et al. A dose-escalation study of the safety, tolerability, and pharmacokinetics of intravenous gatifloxacin in healthy adult men. Pharmacotherapy **2000**;20:49S-58S.

COMMENTS ON BRISTOL-MYERS SQUIBB'S LABELING CHANGES:
The following comments refer to a 22-page PDF document from Bristol-Myers Squibb containing their labeling revisions. It was emailed by BMS to Diana Willard on May 10, 2002 and forwarded to ODS on May 15, 2002.

I. Subsections under **CLINICAL PHARMACOLOGY**

- Page 5: **Glucose Homeostasis**: ODS will defer to clinical pharmacologists for proposals on the best wording to cover the clinical pharmacology studies summarized in this paragraph. However, we do feel that the wording in this paragraph and the first paragraph under **WARNINGS: Changes in Blood Glucose** on page 11 (see section II below) should be consistent, and the fact that symptomatic hypoglycemia occurred in some patients should be included here.

- Page 7: **Glyburide** under **Drug-Drug Interactions**: ODS recommends that the phrase in parentheses in the last sentence be changed to "(see **CLINICAL PHARMACOLOGY: Glucose Homeostasis** and **WARNINGS**)". The current phrase says only "see **CLINICAL PHARMACOLOGY**" but needs to refer to the exact subsection since it itself is located under **CLINICAL PHARMACOLOGY**.

II. New **Changes in Blood Glucose** subsection under **WARNINGS** (Page 11)

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COMMENTS ON BRISTOL-MYERS SQUIBB'S LABELING CHANGES, cont'd.

III. Subsections under **PRECAUTIONS**

- [redacted]
- **Information for Patients:** ODS thinks BMS's revisions are acceptable.
- Page 14: **Drug Interactions:** ODS thinks BMS's revisions are acceptable.
- Page 15: **Geriatric Use:** ODS recommends adding the word "elderly" before "patients" in the second insertion.
- [redacted]

IV. New paragraph under **ANIMAL PHARMACOLOGY** (Page 20)

- ODS chooses not to comment on this section, which relates only to preclinical findings.

V. **Patient Information** section

- [redacted]

COMMENTS ON BRISTOL-MYERS SQUIBB'S EDUCATIONAL PROGRAM:
The following comments refer to a one-page Word document with a two-page attachment from Bristol-Myers Squibb describing their educational program on gatifloxacin-associated changes in glucose homeostasis. The two documents were emailed by BMS to Diana Willard on May 10, 2002 and forwarded to ODS on May 15, 2002.

- ODS thinks it is very important to communicate these new labeling changes, since no published cases of gatifloxacin-associated hyperglycemia or hypoglycemia appear in PubMed (see **LITERATURE**). ODS is encouraged that BMS representatives "will proactively incorporate updated safety information on every call" to healthcare providers and pharmacies beginning on May 13th. Our concern is that the representatives adequately discuss "other patients at risk", including elderly patients "who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems, and/or [be] taking concomitant medications associated with hyperglycemia". It would be helpful if we could see a copy of the Safety Update flashcard which discusses patients at risk.
- [redacted]

REVIEWER'S SIGNATURE / DATE:	TEAM LEADER'S SIGNATURE / DATE:
/S/ 6/5/02	/S/ 6/7/02
Sarah J. Singer, R.Ph.	Debra E. Boxwell, Pharm.D.
DIVISION DIRECTOR SIGNATURE / DATE:	
/S/ 6/10/02	
Julie Beitz, M.D.	

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

/s/

Sarah Singer
6/13/02 09:58:46 AM
PHARMACIST

Julie Beitz
6/14/02 04:43:32 PM
DIRECTOR