MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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FROM: Lanh Green, RPh, MPH
Team Leader, Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

Douglas Shaffer, MD, MHS
Medical Epidemiologist
Bioterrorism Preparedness Team, HFD-970

Lynette Swartz, MEd, MBA/CIS
Technical Information Specialist
Division of Medication Errors and Technical Support, HFD-420

THROUGH: Julie Beitz, MD, Director
Division of Drug Risk Evaluation, HFD-430

TO: David Orloff, MD, Director
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Adverse Event - Congestive heart failure requiring hospitalization
Drug - Pioglitazone (Actos®), Rosiglitazone (Avandia®)

Executive Summary

Thiazolidinediones (TZDs) are used in the treatment of type 2 diabetes mellitus (DM). Type 2 diabetes, most commonly seen in adults, is usually caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.[1] Two TZDs are currently marketed in the United States: pioglitazone (Actos®) and rosiglitazone (Avandia®). Troglitazone (Rezulin®), the first in this class, was withdrawn from the market in March 2000 due to hepatic toxicity.

We retrospectively evaluated case reports of heart failure resulting in hospitalization associated with pioglitazone and rosiglitazone in the FDA Adverse Events Reporting System (AERS).[7]

Forty-seven reports of serious TZD-associated CHF were analyzed (Table 1). Half of the reports represent older females (N=16/Total=28 > 65 years). Fifty-five percent (N=26/Total=47) of the reports describe "New Onset" CHF. "New Onset" includes both reports specifically noting in the narrative that the CHF was new onset as well as those reports <u>not</u> describing existing CHF in the narrative or past medical history. The remaining 45% (N=21/Total=47) of reports describe exacerbation of stable CHF due to edema or excessive weight gain.

Data from this case series provides evidence that TZDs may be associated with CHF to an extent not clearly defined in the product labels. A causal link between the TZD and CHF onset can not be established due to the uncontrolled nature and confounding factors in a spontaneous reporting system. Additionally, the possibility exists that TZD initiation may facilitate a subsequent diagnosis of CHF, due to increased medical monitoring of the patient.

Findings:

1) Postmarketing reports of TZD-associated CHF resulting in hospitalization exist.
2) This case series suggests CHF may be occurring in individuals without previously diagnosed disease.
3) These reports suggest TZDs may be associated with CHF to an extent not clearly defined in the product labels.

Recommendations:

1) Both the pioglitazone and rosiglitazone labels should include mention of these postmarketing reports (see discussion).
2) Additional studies (e.g., Phase IV cohort study to evaluate possible increased risk of incident CHF among both

pioglitazone and rosiglitazone users relative to other oral hypoglycemic medications) should be considered. These studies would further delineate the relationship of thiazolidinediones and congestive heart failure and potential differences between the two marketed drugs in this class.

Background:

Thiazolidinediones (TZDs) are used in the treatment of type 2 diabetes mellitus (DM). Type 2 diabetes, most commonly seen in adults, is usually caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.[1] Two TZDs are currently marketed in the United States: pioglitazone (Actos®) and rosiglitazone (Avandia®). Troglitazone (Rezulin®), the first in this class, was withdrawn from the market in March 2000 due to hepatic toxicity. In clinical studies of healthy volunteers and patients with type 2 diabetes, TZDs were noted to increase median plasma volume and cause mild to moderate edema. In addition, preclinical studies of TZDs demonstrated plasma volume expansion and pre-load-induced cardiac hypertrophy.[1] Finally, cases of TZD-associated CHF have appeared in peer-reviewed literature.[2,3]

The potential for TZDs to "cause fluid retention, which may exacerbate or lead to heart failure" is noted in both the pioglitazone and rosiglitazone labels.[4,5] Earlier, an ODS consult for pioglitazone suggested that a case series of 114 cases of CHF warranted a change in labeling (Attachment 1). More recently in April 2002, both TZD labels were revised to include a statement "Physicians and patients with diabetes are alerted to the possibility of fluid retention when either drug is used as monotherapy or in combination with insulin. The fluid retention may lead to, or exacerbate, congestive heart failure" in Warnings, Precautions, and Adverse Reactions.

In that there appears to remain uncertainty with regard to the propensity for TZDs to cause more serious cases of CHF, we

systematically evaluated reports, submitted through the MedWatch program[6] to the Adverse Event Reporting System (AERS),[7] of CHF in diabetics receiving TZDs.

We specifically aimed to review TZD-associated cases of CHF resulting in hospitalization. Furthermore, we sought to examine what proportion may be associated with "New Onset" CHF and the pharmacoepidemiological factors associated with the CHF report.

Methods:

We retrospectively evaluated case reports of heart failure, edema, and weight gain associated with pioglitazone and rosiglitazone in the FDA Adverse Events Reporting System (AERS). In an effort to concentrate upon reports associated with heart failure, our search criteria used the high level search term, ***"Heart Failure"*** as defined by the Medical Dictionary for Regulatory Activities Terminology (MedDRA™, version 2.0. International Federation of Pharmaceutical Manufacturers Associations). Briefly, this term includes four sub-categories: Heart Failure, Left Ventricular Failure, Right Ventricular Failure, and Heart Failure Symptoms and Signs.

The data query incorporated the month of market approval (May 6 and July 7, 1999 for rosiglitazone and pioglitazone, respectively) through August 6, 2001. We limited the search to reports categorized as having a serious outcome (death, hospitalization, life-threatening, disability, and congenital anomaly) as established by the Code of Federal Regulations [21 CFR 310.301 (b)]. Information extracted from the reports included general characteristics (drug, event date, report origin), demographic/anthropometric data, concomitant diabetic and cardiac drugs, comorbid disease states, and diagnostic tests (chest X-ray, electrocardiogram) information. All reports were included regardless of nationality. Only duplicate reports or follow-up submissions were excluded. This resulted in 443 reports.

In that this number includes a large proportion of foreign reports as well as reports associated with less serious outcomes (e.g. edema), we further limited the case series to domestic cases associated with hospitalization. This resulted in our final case series reported in this consultation report.

Two individuals (Douglas Shaffer, Lanh Green) reviewed all cases and extracted data. All reports were confirmed by independent review. Routine statistical procedures were used for descriptive purposes for comparing report characteristics. Continuous variables are reported as mean (standard deviation), and categorical variables are reported as percentage (frequency). All figures for variables reported are based upon the occurrence or mention in the case report. PC SAS v8.02 (The SAS Institute, Cary, NC) was used for all statistical procedures and carried out by Lynette Swartz from Division of Medication Errors and Technical Support, HFD 420.

Results:

Forty-seven reports of TZD-associated CHF were analyzed (Table 1). Half of the reports represent older females (N=16/Total=28 > 65 years). Fifty-five percent (N=26/Total=47) of the reports describe "New Onset" CHF. "New Onset" includes both reports specifically noting in the narrative that the CHF was new onset as well as those reports <u>not</u> describing existing CHF in the narrative or past medical history. The remaining 45% (N=21/Total=47) of reports describe exacerbation of stable CHF due to edema or excessive weight gain.

The average daily dose was within the ranges recommended in the product labels [(pioglitazone = 29 mg (SD= 12.0) and rosiglitazone = 6.7 mg (SD=2.9)]. The mean time to hospitalization, defined as the duration between initiation of TZD and hospitalization, could be calculated for 17 pioglitazone and 21 rosiglitazone reports. The mean was 94 days for pioglitazone and 84 days for rosiglitazone ranging from one week

to a year for both drugs. The cases represent individuals with refractory diabetes. This is evidenced by concomitant use of other diabetic medications in 34 of 47 cases. In addition, 34% of the reports noted insulin as a concomitant medication. Comorbid CHF risk factors were commonly described: 64% hypertension, 43% coronary artery disease; and 64% other (e.g. previous myocardial infarction, hyperlipidemia, smoker).

Twenty-nine cases (61%) experienced improvement of symptoms (positive de-challenge) upon TZD discontinuation and treatment while 14 cases (29%) continued TZDs and remained symptomatic despite treatment with diuretics. Overall, there was one fatality for rosiglitazone related to congestive heart failure (NYHA Class 1), non-cardiogenic pulmonary edema, and multi-organ failure.

Discussion:

Data from this case series provide evidence that TZDs may be associated with CHF to an extent not clearly defined in the product labels. The development of symptoms leading to hospitalization nearly three months after initiation of drug therapy may suggest an insidious pathophysiological process that could be consistent with fluid retention as opposed to a more direct cardiac effect. A high percentage (61%) of cases was observed with symptomatic improvement of CHF when TZDs were discontinued and diuretic therapy initiated. It is plausible that cases still on TZD therapy (29%) would benefit from improvement of CHF symptoms if TZDs were discontinued.

A causal link between the TZD and CHF onset can not be established due to the uncontrolled nature and confounding factors in a spontaneous reporting system. Additionally, the possibility TZD initiation facilitated CHF diagnosis that may have occurred in the future exists. Regardless, this case series strongly supports the hypothesis that TZDs, as a class, may be

associated with CHF in diabetics, particularly in those with concomitant CHF risks but without diagnosed disease.

Our consultation warrants consideration on three levels. First, attention to these postmarketing reports in the product labels should be given. This may include wording such as, "Postmarketing reports of thiazolidinedione use in diabetic patients have been associated with hospitalization for newly diagnosed congestive heart failure." Second, clinicians should be aware of reports of TZDs in diabetics hospitalized with CHF. Finally, additional observational studies evaluating the risks of CHF in diabetics receiving TZDs should be considered (e.g., Phase IV cohort study). These would be complimentary to ongoing randomized controlled trials.[8,9,10,11]

Findings:

1) Postmarketing reports of TZD-associated CHF resulting in hospitalization exist.
2) This case series suggests CHF may be occurring in individuals without previously diagnosed disease.
3) These reports suggest TZDs may be associated with CHF to an extent not clearly defined in the product labels.

Recommendations:

1) Both the pioglitazone and rosiglitazone labels should include mention of these postmarketing reports (see discussion)
2) Additional studies (e.g., Phase IV cohort study to evaluate possible increased risk of incident CHF among both pioglitazone and rosiglitazone users relative to other oral hypoglycemic medications) should be considered to further delineate the relationship of thiazolidinediones and congestive heart failure and potential differences between the two marketed drugs in this class.

Table 1. Domestic Case Reports of Pioglitazone and Rosiglitazone-Associated Congestive Heart Failure Resulting in Hospitalization*

	Ovefall [N=47]	Pioglitazone [N=22]	Rosiglitazone [N=25]
Demography			
Mean Age (years)	69 (N=41)	65 (N=17)	72 (N=24)
Female	28	14	14
CHF Classification			
New Onset	26	13	13
Exacerbation	21	9	12
Therapy			
Mean Dose (mg)	N/A	29 (N=18)	6.7 (N=21)
Mean Time to Hospitalization (days)	89 (N=38)	94 (N=17)	84 (N=21)
Diabetic Status			
TZD Monotherapy	5	1	4
TZD+Insulin (I)	6	3	3
TZD+Oral Hypoglycemics (OH)	19	7	12
TZD+ OH + I	9	5	4
Unknown OH + I	7	5	2
Unknown I	1	1	0
Co-morbid Risk Factors			
Hypertension	30	14	16
Coronary Artery Disease	20	8	12
Other**	30	13	17
Selected Outcomes			
Positive de-challenge	29 (N=43)	13 (N=18)	16 (N=24)
Symptoms continued with ongoing TZD	14 (N=43)	5 (N=18)	8 (N=24)
Fatality	1	0	1

* All numerical values represent numbers of cases unless otherwise noted.

** Eight additional risk factors: acute myocardial infarction (MI), hematological abnormalities, hyperlipidemia, hypothyroidism, idiopathic CHF, old MI, other cardiovascular diseases, and smoker.

Lanh Green, RPh, MPH

Douglas Shaffer, MD, MHS

Lynette Swartz, MEd, MBA/CIS

References

[1] Physicians' Desk Reference (web). PDR® Electronic Library™ (http://www.pdrel.com). Medical Economics Company, Inc. 2001.

[2] Krentz A, Bailey C, Melander A. Thiazolidines for type 2 diabetes. *BMJ* 200;321:252-253.

[3] Thomas M, Lloyd S. Pulmonary edema associated with rosiglitazone and troglitazone. Letter to the Editor. *Annals of Pharmacotherapy*. 2001:35:123.

[4] Actos (pioglitazone) professional labeling 2002, Takeda Pharmaceuticals America, Inc and Eli Lilly and Co.

[5] Avandia (rosiglitazone) professional labeling, 2002. GlaxoSmithKline.

[6] Kessler D. Introducing MedWatch - a new approach to reporting medication and device effects and product problems. *JAMA* 1993;269(21):2765-2768.

[7] Adverse Event Reporting System(AERS), Rockville, MD: Center for Drug Evaluation and Research, Food and Drug Administration (accessed July 8, 2002, at http://www.fda.gov/cder/aers/default.htm)

[8] Halimi S, Charpentier G, Grimaldi A, et al. Effect on compliance, acceptability of blood glucose self-monitoring and HbA (1c) of a self-monitoring system developed according patient's wishes. The ACCORD study. *Diabetes Metab* 2001;27(6):681-7.

[9] Alderman EL, et al. The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll* Cardiol 2000;35(5):1122-9.

[10] Actos Study No. 01-00-TL-OPI-504 entitled "A randomized, double-blind, comparator-controlled, study of pioglitazone vs. glyburide in the treatment of subjects with Type 2 (non-insulin dependent) diabetes mellitus and mild to moderate congestive heart failure." Takeda Pharmaceuticals North America.

[11] Actos Study No. 01-00-TL-OPI-520 entitled " A randomized, double-blind, comparator-controlled, study of pioglitazone vs. glyburide in the treatment of subjects with Type 2 (non-insulin dependent) diabetes mellitus and mild cardiac disease (NYHA I)." Takeda Pharmaceuticals North America.