

February 2007

GlaxoSmithKline Three Franklin Plaza P.O. Box 13619 Philadelphia, PA 19101-3619

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Re: Clinical Trial Observation of an Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with Avandia® (rosiglitazone maleate) Tablets for Type 2

Diabetes Mellitus

Dear Health Care Provider:

As part of ongoing efforts to provide appropriate safety information to Health Care Providers, GlaxoSmithKline (GSK) is informing you of recent safety data concerning rosiglitazone-containing products, i.e., Avandia® (rosiglitazone maleate) Tablets, Avandamet® (rosiglitazone maleate and metformin hydrochloride) Tablets, and AvandarylTM (rosiglitazone maleate and glimepiride) Tablets. These products are used in treating type 2 diabetes mellitus. To date, cumulative worldwide post marketing exposure is more than nine million patient years for Avandia, one million patient years for Avandamet, and 33,000 patient years for Avandaryl.

Recently, ADOPT (<u>A Diabetes Outcome</u> and <u>Progression Trial</u>) was completed. ADOPT was a randomized, double-blind, parallel group study of patients with recently diagnosed type 2 diabetes mellitus whose progression of diabetes was followed for 4-6 years. The primary goal of the study was to compare glycemic control with rosiglitazone relative to metformin and to glyburide monotherapies in 4,360 randomized patients. The results of ADOPT were published in the *New England Journal of Medicine* (Kahn *et al.*, 2006. N Engl J Med, Vol. 355, No. 23:2427-2443).

A review of the safety data in ADOPT was consistent, in general, with the known safety profile of rosiglitazone. However, significantly more female patients who received rosiglitazone experienced fractures than did female patients who received either metformin or glyburide (see table on the following page). The observed incidence of fractures for male patients in ADOPT was similar among the three treatment groups.

The majority of fractures observed in female patients who received rosiglitazone during ADOPT were in the upper arm (humerus), hand, or foot (see table on the following page). These sites of fracture are different from those associated with post-menopausal osteoporosis (e.g., hip or spine). In ADOPT, the number of female patients with a hip or spine fracture was low and similar among the three treatment groups.

Patients with Fractures in ADOPT

	Rosiglitazone		Metformin		Glyburide	
	811 Males		864 Males		836 Males	
MALE PATIENTS	2766.7 PY		2957.6 PY		2612.8 PY	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture	32 (3.95)	1.16	29 (3.36)	0.98	28 (3.35)	1.07
FEMALE PATIENTS	645 Females		590 Females		605 Females	
	2187.2 PY		1948.0 PY		1630.8 PY	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture *	60 (9.30)	2.74	30 (5.09)	1.54	21 (3.47)	1.29
Lower limb **	36 (5.58)	1.65	18 (3.05)	0.92	8 (1.32)	0.49
Hip	2 (0.31)	0.09	2 (0.34)	0.10	0	0
Foot	22 (3.41)	1.01	7 (1.19)	0.36	4 (0.66)	0.25
Upper limb ***	22 (3.41)	1.01	10 (1.70)	0.51	9 (1.49)	0.55
Hand	8 (1.24)	0.37	4 (0.68)	0.21	1 (0.17)	0.06
Humerus	5 (0.78)	0.23	0	0	0	0
Spine	1 (0.16)	0.05	1 (0.17)	0.05	1 (0.17)	0.06
Other	5 (0.78)	0.23	4 (0.68)	0.21	4 (0.66)	0.25

Rate/100 PY = Patients with Events per 100 Patient Years, n = number of patients

At GSK's request, an independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial. The primary purpose of that study is to investigate cardiovascular endpoints in patients with type 2 diabetes mellitus. The results of the preliminary analysis were reported to GSK as being consistent with the observations from ADOPT. The independent safety committee also recommended that the study continue without modification. Final results of this study are anticipated to be available in 2009.

Presently, our understanding of the clinical significance of the findings from these two long-term trials is incomplete, and the mechanism(s) for the observed increase in fractures is uncertain. Further evaluation of these observations is ongoing. GlaxoSmithKline believes the risk of fracture should be considered in the care of patients, especially female patients, with type 2 diabetes mellitus who are currently being treated with rosiglitazone, or when initiation of rosiglitazone treatment is being considered. In these patients, as with all patients with type 2 diabetes mellitus, attention should be given to assessing and maintaining bone health according to current standards of care.

GlaxoSmithKline is committed to providing Health Care Providers and patients with up-to-date and accurate information regarding our products. You can assist GSK in monitoring the safety of our products by reporting adverse reactions to GSK at 1-888-825-5249 or to the FDA MedWatch program (telephone 1-800-332-1088, fax 1-800-332-0178, online at www.fda.gov/medwatch, or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787).

Should you have any questions or require additional information, please contact your local GlaxoSmithKline information line (1-888-825-5249).

Sincerely,

Alexander R Cobitz, MD, PhD Senior Director Metabolism

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Clinical Development and Medical Affairs

GlaxoSmithKline

Enclosure: Complete Prescribing Information for Avandia® Tablets.

^{*} Some patients experienced fractures in more than one category.

^{**} Other sites of fracture included: ankle, femur, fibula, lower limb (general), patella, and tibia.

^{***} Other sites of fracture included: clavicle, forearm, radius, upper limb (general), and wrist.