GlaxoSmithKline

7th March, 2007

Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with Avandia® (rosiglitazone maleate)

Dear Health Care Provider:

In agreement with European Regulatory Authorities, 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 Avaglim® (rosiglitazone maleate and glimepiride) Tablets. The information could be summarized as follows:

- **Clinical trial data (ADOPT) show that female patients treated with rosiglitazone experienced significantly more fractures in feet, hands and upper arms (humerus) than female patients who received either metformin or glyburide.**
- **The mechanism for the observed increase in fractures is uncertain. Further evaluation of these findings is ongoing.**
- **The risk of fracture should be considered in the care of in particular female patients treated with rosiglitazone.**

Recently, the clinical trial ADOPT (A Diabetes Outcome and Progression Trial) was completed. ADOPT was a randomised, 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 glycaemic control with rosiglitazone relative to metformin and to glibenclamide monotherapies in 4,360 randomised 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 glibenclamide (see table on 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 foot, hand , and the arm . 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	
MALE PATIENTS	811 Males 2766.7 PY		864 Males 2957.6 PY		836 Males 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 2187.2 PY		590 Females 1948.0 PY		605 Females 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

Rate/100 PY = Patients with Events per 100 Patient Years, n = number of patients
* Some patients experienced fractures in more than one category.

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 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. The risk of fracture should be considered in the care of patients, in particular female patients who are currently being treated with rosiglitazone, or when initiation of rosiglitazone treatment is being considered. In these patients attention should be given to assessing and maintaining bone health according to current standards of care.

Your reporting of suspected adverse reactions/events in patients treated with rosiglitazone to GSK Ireland or the Pharmacovigilance Unit of the Irish Medicines Board is most valuable and is strongly encouraged.

Should you have any questions or require additional information, please contact our medical information department on 1800 244 255.

Sincerely,

Martina Dempsey

Martina Dempsey PhD
Director of Medical & Regulatory Affairs