Health Canada Endorsed Important Safety Information on
PrAVANDIA®, PrAVANDAMET® and PrAVANDARYL™

February 23, 2007

Dear Health Care Professional:

Subject: Increased Incidence of Fractures in Female Patients Who Received Long-Term Treatment with AVANDIA® (rosiglitazone maleate) Tablets for Type 2 Diabetes Mellitus

GlaxoSmithKline Inc. (GSK), in consultation with Health Canada, would like to inform you of recent safety data concerning rosiglitazone-containing products, i.e., AVANDIA® (rosiglitazone maleate) tablets, AVANDAMET® (rosiglitazone maleate/metformin hydrochloride) tablets and AVANDARYL™ (rosiglitazone maleate/glimepiride) tablets. These products are used in treating type 2 diabetes mellitus.

Recently, ADOPT[1] (A Diabetes Outcome and Progression Trial) 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.

- In the ADOPT study, significantly more female patients who received rosiglitazone experienced fractures than did female patients who received either metformin or glyburide (9.3% vs. 5.1% and 3.5% respectively). The majority of these fractures were in the upper arm (humerus), hand, or foot. These fracture sites are different from those associated with post-menopausal osteoporosis (e.g., hip or spine). The observed incidence of fractures for male patients was similar among the three treatment groups.
- 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, or when initiation of rosiglitazone treatment is being considered.

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. 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. 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
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

* 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.

At GSK's request, an independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial, which compared rosiglitazone in combination with either metformin or sulfonylurea to combination therapy with metformin and sulfonylurea. 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, with the exception of more detailed fracture data capture. 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.

GSK will continue to review new safety data for Avandia®, including post-marketing adverse event reports. GSK will be working with Health Canada to further integrate new safety information in the Canadian Product Monograph.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious fracture or other serious or unexpected adverse reactions in patients receiving Avandia®, Avandamet® or Avandaryl™ should be reported to GlaxoSmithKline or Health Canada at the following addresses:

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
Tel.: 1-800-387-7374

Any suspected adverse reaction can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties.*

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS)
bmors_enquiries@hc-sc.gc.ca
Tel: (613) 941-3171
Fax: (613) 941-1365

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Any questions from health care professionals may be directed to our Medical Information department via GSK Customer Service at 1-800-387-7374.

Sincerely,

Dr. John A Dillon, MB BCh MFPM
VP, Medical Division and Chief Medical Officer
GlaxoSmithKline Inc.

REFERENCES

[1] Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. New Engl J Med. 2006;355:2427-2443.