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

GlaxoSmithKline

June 1, 2007

Dear Health Care Professional:

Subject: Cardiac Safety of Avandia® (rosiglitazone maleate).

An article in the New England Journal of Medicine (NEJM) on May 21, 2007, has generated significant public attention on the cardiac safety of Avandia®, Avandamet® and Avandaryl™. The Nissen & Wolski article[1], based on a meta-analysis of 42 clinical studies, noted a statistically significant increased risk of myocardial infarction (OR 1.43, CI 1.03-1.98, p = 0.03) and a statistically non-significant increase in the risk of cardiovascular death (OR 1.64, CI 0.98-2.74, p = 0.06) associated with the use of rosiglitazone in comparison to the use of a placebo or other anti-diabetic therapies.

The conclusions reached require confirmation. Analysis of all currently available data is ongoing and findings will be communicated when review is complete.

Some of the studies in the NEJM article included patients using rosiglitazone in combination with other anti-diabetic therapies. Some of these combinations, specifically rosiglitazone + metformin + sulfonylurea or rosiglitazone + insulin are not approved for use in Canada.

Important Advice for Managing Your Patients

- In Canada, Avandia® is NOT approved for use:
  - with insulin therapy
  - with the combination of metformin AND a sulfonylurea
  - in patients with pre-diabetes.
- Avandia® is contraindicated in patients with NYHA Class III and IV cardiac status.
- Avandia® should be used with caution in any patient with NYHA Class I and II cardiac status.
- All patients should be monitored for signs and symptoms of fluid retention, edema, and rapid weight gain.
- The dose of Avandia® used in combination with a sulfonylurea should not exceed 4mg daily.

When considering treatment decisions, physicians are recommended to carefully weigh the overall benefit versus the risk of Avandia®, Avandamet® or Avandaryl™ for each individual patient.

In Canada, Avandia® is indicated for[2]:

- use as monotherapy, in patients not controlled by diet and exercise alone, to reduce insulin resistance and lower elevated blood glucose in patients with type 2 diabetes mellitus.
- use in combination with metformin or a sulfonylurea when diet and exercise plus the single agent do not result in adequate glycemic control. For patients inadequately controlled on metformin or a sulfonylurea, Avandia® should be added to, not substituted for, metformin or the sulfonylurea.

Currently, the Canadian Product Monograph also contains the following statement in the Warnings and Precautions section:

Cardiovascular and Edema

Thiazolidinediones, like Avandia®, alone or in combination with other antidiabetic agents, can cause fluid retention, which can exacerbate or lead to congestive heart failure. The fluid retention may very rarely present as rapid and excessive weight gain. All patients should be monitored for signs and symptoms of adverse reactions relating to fluid retention and heart failure. In particular, patients who are at risk for heart failure including those receiving concurrent therapy which increases insulin levels (i.e. sulfonylureas), and those patients with mild to moderate heart failure (NYHA Class I and II) should be closely monitored.

Treatment with thiazolidinediones has been associated with cases of congestive heart failure, some of which were difficult to treat unless the medication was discontinued. Avandia® should be discontinued if any deterioration in cardiac status occurs.

As a result of an ongoing regulatory review, the Product Monograph for Avandia® is currently being updated to include additional information on cardiac safety, and that the dose of Avandia® used in combination with a sulfonylurea should not exceed 4mg daily.

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. As always, any serious or unexpected adverse reactions in patients receiving Avandia® 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)
E-mail: 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,

Original signed by

Ravinder Kumar, Ph.D.
Vice President, Regulatory Affairs
GlaxoSmithKline Inc.

Avandia® and Avandamet® are registered trademarks, used under license by GlaxoSmithKline Inc.

Avandaryl™ is a trademark, used under license by GlaxoSmithKline Inc.

References

1. Nissen SE, Wolski, K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356. DOI: 10.1056/NEJMoa072761.
2. Product Monograph of AVANDIA®. GlaxoSmithKline Inc. November 2006.