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

November 1, 2007

Dear Health Care Professional:

Subject: **New restrictions on the use of rosiglitazone products due to cardiac safety concerns (AVANDIA®, AVANDAMET® and AVANDARYL™)**

GlaxoSmithKline Inc., in consultation with Health Canada, would like to inform you of important new restrictions on the treatment of type 2 diabetes mellitus with the rosiglitazone-containing products: AVANDIA® (rosiglitazone), AVANDAMET® (rosiglitazone and metformin), and AVANDARYL™ (rosiglitazone and glimepiride).

Further to a Health Canada assessment of adverse event reports, published articles* and other available information on congestive heart failure, myocardial infarction, and related events, the Canadian Product Monographs for rosiglitazone-containing products are being updated and will include the following new usage restrictions:

- **Rosiglitazone (AVANDIA®) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated.**
- **Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated.**
- **Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV).**

Also, as a reminder:

- **Rosiglitazone is not indicated for use with insulin.** This combination is associated with an increased risk of heart failure.
- **Rosiglitazone is not indicated for triple therapy** (i.e., therapy with rosiglitazone in combination with both metformin and a sulfonylurea). Increases in congestive heart failure and other fluid retention-related events have been reported in patients receiving rosiglitazone as part of triple therapy.

Dual therapy

When adequate glycemic control is not obtained through diet and exercise plus monotherapy, then rosiglitazone can be used in dual therapy, as follows:

- use in combination with metformin; or
- when metformin is contraindicated or not tolerated, use in combination with a sulfonylurea.

Rosiglitazone can be added to (not substituted for) the monotherapy agent.

Other new information in the Product Monographs will include clinical trial evidence regarding cardiac ischemic events associated with rosiglitazone.

Patients are being advised to talk to their doctors about the risks of continuing rosiglitazone therapy if they have underlying heart disease, or are at high risk of heart attack or heart failure (see the Public Communication associated with this Letter, to be posted at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/2007/index_e.html).

As soon as they are available, the revised Product Monographs for AVANDIA®, AVANDAMET® and AVANDARYL™ will replace the versions dated July 2007 (AVANDAMET® and AVANDARYL™) and October 2007 (AVANDIA®) that are posted at www.gsk.ca.

* Recent publications include:

1. **Singh**, S., Loke, Y.K., & Furberg, C.D., JAMA (2007) 298:1189 Long-term Risk of Cardiovascular Events with Rosiglitazone: A Meta-analysis.
2. **Nissen**, S.E. & Wolski, K., NEJM (2007) 356:2457 Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes.
3. **Home**, P.D., et al., & The RECORD Study Group, NEJM (2007) 357:28 Rosiglitazone Evaluated for Cardiovascular Outcomes – An Interim Analysis.
4. **Kahn**, S.E., et al., NEJM (2006) 355:2427 Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy (The ADOPT Study).

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®, AVANDAMET® and 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
www.gsk.ca

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:
Marketed Health Products Directorate (MHPD)
E-mail: MHPD_DPSC@hc-sc.gc.ca
Tel: (613) 954-6522; Fax: (613) 952-7738
http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html

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

Dr. Tjark Reblin, MD, MBA
Vice President, Medical Division and Chief Medical Officer
GlaxoSmithKline Inc.