

**Health Canada Endorsed Information on Important New Restrictions on the use of rosiglitazone
(^{Pr}AVANDIA[®], ^{Pr}AVANDAMET[®] and ^{Pr}AVANDARYL[®])**



November 9, 2010

Dear Health Care Professional:

Subject: Important new restrictions on the use of rosiglitazone products due to information on cardiovascular related events (AVANDIA[®], AVANDAMET[®] and AVANDARYL[®])

GlaxoSmithKline Inc., in consultation with Health Canada, would like to inform you of important new restrictions on the use of AVANDIA[®] (rosiglitazone), AVANDAMET[®] (rosiglitazone and metformin), and AVANDARYL[®] (rosiglitazone and glimepiride) for the treatment of type 2 diabetes mellitus.

Further to a Health Canada assessment of recent data collected from a meta-analysis of clinical trials¹ and from some observational studies^{2,3} suggesting an elevated risk of cardiovascular events in patients treated with AVANDIA[®], there are new usage restrictions on rosiglitazone-containing products, as follows:

AVANDIA[®]/AVANDAMET[®]/AVANDARYL[®] is now indicated only in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance.

Prior to starting or renewing a prescription for AVANDIA[®]/AVANDAMET[®]/ AVANDARYL[®], physicians should consider whether a rosiglitazone-containing product is an appropriate therapeutic choice, and if so:

- **Document the eligibility of patients to meet the above criteria;**
- **Counsel each patient on the risks and benefits of AVANDIA[®]/AVANDAMET[®]/ AVANDARYL[®], including the cardiovascular risks; and**
- **Obtain the patient's written informed consent to take the drug (see attached).**

The Canadian Product Monographs for rosiglitazone-containing products have been updated to reflect the new indication and informed consent process. **Also, note that a new boxed warning has been added to the Canadian Product Monographs with the following information:**

- Rosiglitazone-containing products, like other thiazolidinediones, can cause fluid retention and congestive heart failure.
- Rosiglitazone-containing products may be associated with an increased risk of cardiac ischemia. **AVANDIA®/AVANDAMET®/AVANDARYL® is not recommended in patients with a history of ischemic heart disease, particularly those with myocardial ischemic symptoms.**
- Rosiglitazone-containing products should be used only when all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance.

Physicians are advised to counsel new and currently treated patients about the risks of initiating and/or continuing rosiglitazone therapy and obtain their written informed consent as described above. Copies of the informed consent and consumer information for AVANDIA®, AVANDAMET® and AVANDARYL® are attached and will be available at www.gsk.ca, or may be ordered by contacting GSK Customer Service at 1-800-387-7374.

Pharmacists can continue to dispense AVANDIA®, AVANDAMET® and AVANDARYL® to patients and should refer patients to their physician for advice on their treatment.

A Public Communication will be issued to inform patients about these changes, and will advise patients to make an appointment with their doctor as soon as possible to revisit their treatment, rather than abruptly stopping their medication.

The Product Monographs for AVANDIA®, AVANDAMET® and AVANDARYL® will also include additional cardiovascular information and once available will replace the versions dated March 2009 (AVANDIA® and AVANDAMET®) and May 2009 (AVANDARYL®). The revised Product Monographs for AVANDIA®, AVANDAMET® and AVANDARYL® will be available at www.gsk.ca and Health Canada's Drug Product Database (<http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/databasdon/index-eng.php>)

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 or unexpected adverse reactions in patients receiving AVANDIA®, AVANDAMET® and AVANDARYL® should be reported to GlaxoSmithKline Inc. or Health Canada at the following addresses:

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario L5N 6L4
Telephone: 1-800-387-7374
www.gsk.ca

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
 - o Fax toll-free to 1-866-678-6789, or
 - o Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (<http://www.hc-sc.gc.ca/dhp-mpps/medeff/report-declaration/index-eng.php>). The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties*.

For other health product inquiries related to this communication, please contact Health Canada at:

Canada Vigilance National Office
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario K1A 0K9
E-mail: CanadaVigilance@hc-sc.gc.ca
Telephone: 866 234 2345
Fax: 866 678 6789

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

Avandia®, Avandamet® and Avandaryl® are registered trademarks, used under license by GlaxoSmithKline Inc.
Attachments: Informed Consent and Consumer Information for AVANDIA®, AVANDAMET® and AVANDARYL®

References

1. Nissen S, Wolski K. Rosiglitazone Revisited. An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. Arch Intern Med 2010; 170 (14). 1191-1201.
2. Juurlink D, Gomes T, Lipscombe L, Austin P, Hux J, Mamdani M. Adverse Cardiovascular Events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ 2009; 339:b2942.
3. Graham DJ, Quillet-Hellstrom R, MaCurdy TE et al. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone. JAMA 2010;304:411-418.