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IMPORTANT SAFETY INFORMATION REGARDING

AVANDIA® (rosiglitazone maleate)

Dear Health Care Professional,

As you may know, AVANDIA® (rosiglitazone maleate) is an oral agent for the treatment of type 2 diabetes belonging to the thiazolidinedione (TZD) class. AVANDIA® is indicated for use as an adjunct to diet and exercise as monotherapy or in combination with metformin or a sulfonylurea to reduce insulin resistance and lower elevated blood glucose in patients with type 2 diabetes mellitus.

AVANDIA® has been available in the U.S. market since June 1999 and was approved in Canada in March, 2000. Since the U.S. launch of AVANDIA®, over 2 million patients have been treated with AVANDIA® and over 12 million prescriptions have been written.

GlaxoSmithKline Inc. would like to update you on important safety information regarding AVANDIA® to reflect the extensive postmarketing experience of the product since its launch. The Product Monograph has recently been revised to reflect this information. Most of the information summarized below is not new to the Product Monograph. However, to maximize clarity and ensure that AVANDIA® is prescribed optimally by physicians, some changes have been made to the wording or location of specific information. In addition, although AVANDIA® is not currently indicated for use in combination with insulin, the current changes also include relevant safety information regarding this use. A copy of the revised Prescribing Information is attached for your information.

As outlined in the original AVANDIA® Product Monograph under the 'Warnings' section, physicians should be aware that thiazolidinediones can cause fluid retention, which can exacerbate or lead to congestive heart failure. Patients at risk for heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure. AVANDIA® should be discontinued if any deterioration in cardiac status occurs. In addition, AVANDIA® is not indicated in patients with New York Heart Association (NYHA) Class III and IV cardiac status. For further emphasis, this important information regarding NYHA Class III & IV patients has been moved from the 'Precautions' section to the 'Warnings' section of the Product Monograph. In postmarketing experience with AVANDIA®, adverse events potentially related to volume expansion (e.g. congestive heart failure, pulmonary edema and pleural effusions) have been reported. It is important to also note that thiazolidinediones, including AVANDIA®, are contraindicated in patients with acute heart failure. This contraindication is new to the Product Monograph.

AVANDIA® is not currently indicated for use in combination with insulin. In clinical trials evaluating the combination use of AVANDIA® with insulin, an increased incidence of cardiac failure and other cardiovascular adverse events was seen in patients receiving AVANDIA® and insulin compared to insulin alone. It is important to note that these clinical trials included patients with long-standing diabetes (average 12 to 13 years) and a high prevalence of pre-existing medical conditions (e.g., ischemic heart disease 14%, vascular disease 9%, congestive heart failure 2.5%). Patients who experienced heart failure in these trials were on average older, had a longer duration of diabetes and were mostly on the higher 8 mg dose of AVANDIA®. In the insulin combination studies, adverse events of edema were reported. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and AVANDIA®.

Weight gain with thiazolidinediones can result from increases in subcutaneous adipose tissue and/or from fluid retention. Treatment should be re-evaluated in patients with excessive weight gain.

As the safety and effectiveness of rosiglitazone have not been established in patients younger than 18 years of age, AVANDIA® is not indicated for use in this population. Thiazolidinediones promote the maturation of preadipocytes and have been associated with weight gain. Obesity is a major problem in adolescents with type 2 diabetes. Further, as there are no controlled trials of AVANDIA® in pregnant women, AVANDIA® should not be used and is not indicated for use in pregnant women.

Because AVANDIA® does not stimulate insulin secretion, hypoglycemia is not expected to occur when AVANDIA® is prescribed as monotherapy. Patients taking AVANDIA® with other hypoglycemic agents (e.g. insulin secreting agents) may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

GlaxoSmithKline Inc. continues to work closely with Health Canada to monitor adverse event reporting and to ensure that up-to-date information regarding the use of AVANDIA® is available.

The identification, characterization, and management of drug-related adverse events are dependent on the active participation of health care professionals in adverse drug reaction reporting programmes. Any occurrences of adverse cardiac events or other serious and/or unexpected adverse events in patients receiving AVANDIA® should be reported to GlaxoSmithKline or the Bureau of Licensed Product Assessment at the following addresses:

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

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Bureau of Licensed Product Assessment
Therapeutic Products Programme
HEALTH CANADA
Address Locator: 0201C2
Ottawa, Ontario K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in *the Compendium of Pharmaceuticals and Specialties* or on the TPD website, along with the ADR Guidelines at:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.pdf

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 Medical Information via GlaxoSmithKline Customer Service at 1-800-387-7374.

Sincerely,

Anne Phillips, M.D., FRCPC
Vice-President, Research & Development and Chief Medical Officer
GlaxoSmithKline Inc.