Health Canada Endorsed Important Safety Information on ZOFRAN® (ondansetron hydrochloride dihydrate, ondansetron)

October 3, 2012

Dear Healthcare Professional:

Subject: ZOFRAN® (ondansetron hydrochloride dihydrate, ondansetron) - Important new safety information: Dose restriction for intravenous (IV) use due to dose-dependent QT interval prolongation

GlaxoSmithKline Inc., in collaboration with Health Canada, would like to notify you of new information regarding the risk of electrocardiographic QT interval prolongation associated with ZOFRAN® (ondansetron). ZOFRAN® (ondansetron) is indicated in adults of all ages for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and in adults ≤65 years of age for the prevention and treatment of post-operative nausea and vomiting. ZOFRAN® (ondansetron) is also indicated in children 4 years of age and older for the prevention of chemotherapy-induced nausea and vomiting.

A recently completed study identified a dose-dependent prolongation of the corrected QT interval (QTc) among healthy subjects treated with ondansetron. QTc interval prolongation can lead to Torsade de Pointes (TdP), a potentially life-threatening heart rhythm abnormality. Findings and recommendations based on this new study are as follows:

- Ondansetron can cause a dose-dependent prolongation of the electrocardiographic-corrected QT interval (QTc), which can lead to Torsade de Pointes, a potentially life-threatening heart rhythm abnormality.
- The new **maximum** recommended single intravenous (IV) dose of ZOFRAN® is 16 mg infused over 15 minutes.
- The 32 mg IV dose of ZOFRAN® and the 8 mg intravenous dose followed by a 1 mg/hour continuous infusion of ZOFRAN® are no longer recommended and should not be used.
- Avoid ondansetron in patients with congenital long QT syndrome. Use caution if administering ondansetron to patients with other risk factors for QT interval prolongation, such as electrolyte abnormalities, congestive heart failure, bradyarrhythmias or use of other medicines that can lead to either QT prolongation or electrolyte abnormalities.
- Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to ondansetron administration.

The Canadian Product Monograph has been updated to reflect this new safety information. The revised Product Monograph for ZOFRAN® may be accessed on the Health Canada website, at http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

There have been post-marketing reports of QT prolongation and TdP in patients using ondansetron at low and high doses. Ventricular dysrhythmias (including TdP), cardiac arrest, and sudden death have been reported rarely (<0.01%) in the post-market setting among patients using ZOFRAN®. Careful patient selection is necessary as some patients may be at higher risk for these events.

Physicians should assess their patients for risk factors for QT interval prolongation or TdP before prescribing ZOFRAN®. The revised ZOFRAN® Product Monograph contains a list of risk factors for TdP.

For adults treated with intravenous ZOFRAN® prior to chemotherapy, the usual dose is 8 mg infused over 15 minutes at least 30 minutes prior to chemotherapy. ZOFRAN® should not be administered more rapidly than recommended as more rapid infusion can lead to greater QTc prolongation.

There are no changes to recommended oral dosing of ZOFRAN® in adults. There are no changes to recommended oral or intravenous dosing in children.

Patients should be advised to contact their healthcare professional if they experience signs or symptoms of an abnormal heart rate or rhythm while taking ondansetron (e.g., dizziness, palpitations, syncope).

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 QT interval prolongation, ventricular dysrhythmia, cardiac arrest, sudden death, or other serious or unexpected adverse reactions in patients receiving ZOFRAN® should be reported to GlaxoSmithKline Inc. or Health Canada.

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

To correct your mailing address or fax number, contact GlaxoSmithKline.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Should you have any questions or require additional information regarding the use of ZOFRAN®, please contact GlaxoSmithKline Inc., Medical Information Department at 1-800-387-7374.

Sincerely,

Original signed by

Dr. Glenn Crater,
Vice-President, Medical and Chief Medical Officer
GlaxoSmithKline Inc.