Health Canada Endorsed Important Safety Information on PrVOLIBRIS®

July 9, 2012

Dear Healthcare Professional:

Subject: Contraindication regarding the use of VOLIBRIS® (ambrisentan) in patients with Idiopathic Pulmonary Fibrosis (IPF)

GlaxoSmithKline Inc., in consultation with Health Canada, would like to inform you of new safety information regarding the use of VOLIBRIS® in patients with idiopathic pulmonary fibrosis (IPF). Higher rates of disease progression or deaths were observed during a prematurely discontinued clinical trial in IPF patients treated with VOLIBRIS®.

- A clinical study in patients with IPF was prematurely discontinued due to lack of efficacy. Evaluation of the composite primary endpoint revealed higher rates of disease progression (including decreases in respiratory function, respiratory hospitalizations) or deaths in the VOLIBRIS® group versus the placebo group.
- VOLIBRIS® treatment in patients with IPF should be discontinued and the individual patient's treatment should be reassessed promptly.
- VOLIBRIS® is not indicated for IPF; nonetheless, it is now contraindicated in patients with IPF, with or without pulmonary hypertension.

VOLIBRIS® (ambrisentan), a selective endothelin A receptor antagonist, is indicated for the treatment of idiopathic ('primary') pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) in patients with WHO functional class II or III symptoms who have not responded to conventional therapy.

A randomized (2:1), double-blind, placebo-controlled, event-driven clinical trial (ARTEMIS-IPF) of 492 patients with IPF (VOLIBRIS® N=329, placebo N=163) 11% of which had secondary pulmonary hypertension (VOLIBRIS® n=36, placebo n=18), was terminated early due to lack of efficacy. In this study, a higher rate of the composite primary endpoint, disease progression (including decreases in respiratory function, respiratory hospitalizations), or deaths, was observed in the VOLIBRIS® group (90 events, 27%) compared to the placebo group (28 events, 17%). Evaluation of the primary endpoint components indicated that there were higher rates of respiratory hospitalizations, mortality events, and decreases in respiratory function in the VOLIBRIS® group versus placebo.

VOLIBRIS® is *not* indicated for the treatment of IPF; nonetheless, the following new safety information has been added to the Contraindications section of the VOLIBRIS® Product Monograph.

VOLIBRIS® (ambrisentan) is contraindicated in:
•Patients with Idiopathic Pulmonary Fibrosis (IPF), with or without pulmonary hypertension.

Important Information for Healthcare Professionals:
- Healthcare professionals are reminded that the indication for the use of VOLIBRIS® in the treatment of idiopathic ('primary') pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) in patients with WHO functional class II or III symptoms who have not responded to conventional therapy remains unchanged.
- VOLIBRIS® treatment in patients with IPF should be discontinued and the individual patient's treatment should be reassessed promptly.
- Physicians should continue to prescribe VOLIBRIS® treatment in accordance with the approved Product Monograph.

The updated Product Monograph for VOLIBRIS® is available at www.gsk.ca. Any questions from healthcare professionals should be directed to GSK's Medical Information department via the GSK Customer Service at 1-800-387-7374.

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. Serious or unexpected adverse reactions in patients receiving VOLIBRIS® should be reported to GlaxoSmithKline or Health Canada.

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

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:
  - Fax toll-free to 1-866-678-6789, or
  - 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-mps/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:
Marketed Heath Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 1-613-954-6522
Fax: 1-613-952-7738

To change your mailing address or fax number, contact the Market Authorization Holder (GlaxoSmithKline Inc.).

Sincerely,

original signed by

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

Reference:

1. G. Raghu *et al*. ARTEMIS-IPF: A Placebo-Controlled Trial Of Ambrisentan In Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2012;185:A3632.