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Health Canada Endorsed Important Safety Information on VOTRIENT® (pazopanib hydrochloride)

August 6, 2013

Dear Health care Professional:

Subject: VOTRIENT® (pazopanib hydrochloride) - Important Change to Frequency of Serum Liver Test Monitoring for Hepatotoxicity

GlaxoSmithKline Inc., in consultation with Health Canada, would like to inform you of an important safety update to the Warnings & Precautions section of the Product Monograph for VOTRIENT®, regarding a change in frequency of serum liver test monitoring for hepatotoxicity.

- VOTRIENT® (pazopanib hydrochloride) is associated with hepatotoxicity including hepatic failure and fatalities. VOTRIENT® should not be used in patients who have baseline plasma bilirubin concentrations > 1.5 X Upper Limit of Normal (ULN) with direct bilirubin >35% and ALT elevations of >2 X ULN, or who have moderate or severe hepatic impairment (Child Pugh B and C). These are not new recommendations, and remain unaltered from the previously approved Product Monograph.
- Physicians are asked to monitor serum liver tests before initiation of treatment, during treatment with VOTRIENT® and interrupt, reduce or discontinue dosing as recommended in the Product Monograph (see below).
- Testing of serum liver enzyme and bilirubin levels during treatment has increased in frequency to include monitoring during weeks 2, 4, 6, 8 and Months 3 and 4, and as clinically indicated. Periodic monitoring should continue after Month 4.

VOTRIENT® is a tyrosine kinase inhibitor indicated for the treatment of patients with metastatic renal cell (clear cell) carcinoma as first-line systemic therapy or as second line systemic therapy after treatment with cytokines for metastatic disease.

It is also indicated for the treatment of patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease, or who have progressed within 12 months after (neo) adjuvant therapy.

Elevated Serum Liver Tests should be managed as described below and in the Product Monograph (see WARNINGS AND PRECAUTIONS, Hepatic Effects):

- Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on VOTRIENT® with weekly monitoring of liver function until ALT returns to Grade 1 (NCI CTCAE*) or baseline.

- Patients with ALT elevations of >8 X ULN should have VOTRIENT® interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with VOTRIENT® is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT® at a reduced dose of no more than 400 mg once daily and measure serum liver tests weekly for 8 weeks. Following reintroduction of VOTRIENT®, if ALT elevations >3 X ULN recur, then VOTRIENT® should be permanently discontinued.

- If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN, VOTRIENT® should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE*) or baseline. VOTRIENT® is a uridine diphosphate glucuronyltransferase (UGT1A1) inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

- For isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) treatment could continue and dose modification is not required. However, further evaluation for a possible underlying cause should be considered.

- Concomitant use of VOTRIENT® and simvastatin increases the risk of ALT elevations. Concomitant use of VOTRIENT® and statins should be undertaken with caution and close monitoring.

The revised Product Monograph for VOTRIENT® may be accessed on the Health Canada Website at http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp, or on the Canadian Website of GlaxoSmithKline (www.gsk.ca).

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 other serious or unexpected adverse reactions in patients receiving VOTRIENT® should be reported to GlaxoSmithKline or Health Canada.

** NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events*

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

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: 1-613-954-6522
Fax: 1-613-952-7738

If you have any questions about this new information, please contact GlaxoSmithKline Medical Information Department at 1-800-387-7374.

Sincerely,

Original signed by

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