GlaxoSmithKline
Scientific Office

جلاكسو سميث كلاين
المكتب العلمي

ترخيص رقم 00047 – 59 - 32 - 101
رقم العضوية 68583

July 14th , 2013

Title: VOTRIENT™ (Pazopanib) – Important change to frequency of Serum liver test monitoring for hepatotoxicity

Dear Healthcare Professional:

GlaxoSmithKline would like to inform you of an important new recommendation for Pazopanib regarding the frequency of serum liver test monitoring for hepatotoxicity:

Summary:

- Serum liver tests should be monitored more frequently during the first 9 weeks of therapy than originally recommended.
- Serum liver function tests should be carried out before starting treatment with Pazopanib, and now at weeks 3, 5, 7, and 9.
- Subsequent tests should be made at months 3 and 4, and periodically thereafter as indicated.
- If elevated liver enzyme values are found, they should be managed by increased monitoring or temporary or permanent interruption of treatment.
- 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 or baseline.
- Patients with isolated 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 resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Further information on the safety concern:

Pazopanib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma and for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy.

Abnormalities of liver function are commonly associated with Pazopanib (≥ 1/100 to < 1/10) and there have been uncommon (≥ 1/1,000 to < 1/100) cases of hepatic failure, including fatalities. In order to manage this risk, Pazopanib was originally licensed with a requirement for monitoring of liver function at least once every 4 weeks during the first four months of treatment.

The periodic safety review of data from Pazopanib clinical trials has since then identified elevated ALT (>3x the upper limit of normal (ULN)) and concurrent AST (>3xULN) and bilirubin (>2xULN) elevations occurring primarily between weeks 3 and 9 of therapy. A comparison across trials with Pazopanib indicates that 1% of patients treated with Pazopanib had ALT > 3xULN at week 2. Approximately 5 % of

patients had ALT > 3xULN at week 3. Most new cases of ALT > 3xULN occurred by week 9. More frequent monitoring between weeks 3 and 9 may lead to earlier detection of elevated serum liver tests and hepatotoxicity in patients taking Pazopanib.*

The current Summary of Product Characteristics (SPC) will be updated as follows:

Special warnings and precautions for use

Serum liver tests should be monitored before initiation of treatment with Pazopanib and at weeks 3, 5, 7 and 9. Thereafter, monitored at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4.

The letter is sent in agreement with the Saudi Food and Drug Authority

Further Information

GlaxoSmithKline will continue to monitor the safety of Votrient™ (Pazopanib) and update SFDA of any serious adverse event for evaluation. You can assist us in monitoring the safety of Votrient™ (Pazopanib) by reporting adverse reactions to GlaxoSmithKline Fax: +96626536660 or by email to safety email: faisal.m.shujrah@gsk.com or to the National Pharmacovigilance and Drug Safety Center at Fax: +966-11-2057662 or by email to: npc.drug@sfda.gov.sa

If you have any question about the new information, please contact GSK medical information department at GlaxoSmithKline Saudi Arabia by phone: +966 2 6536666 or fax: +966 2 6536660.

Best regards;

Mohammed Hany Soliman
Medical Director
GlaxoSmithKline
Saudi Arabia

Reference:

Votrient™ (Pazopanib) prescribing information

*PBRER - Reporting period: 19 October 2012 to 18 April 2013