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GLAXOSMITHKLINE SAFETY ADVISORY

Date: March 13th 2008

Dear Healthcare Professional,

Title: TYVERB (lapatinib) – hepatotoxicity (predominantly transaminase elevations)

Key Messages

This communication from GlaxoSmithKline is to notify you of important safety information for TYVERB (lapatinib).

GSK has observed that hepatotoxicity (predominantly transaminase elevations) may occur during treatment with TYVERB (lapatinib). Rarely, hepatotoxicity has been severe. Elevated liver enzymes generally returned to normal when patients stopped taking TYVERB (lapatinib).

As of 05 December 2007, approximately 8702 subjects were estimated to have received TYVERB (lapatinib) in clinical trials. Since marketing approval, TYVERB (lapatinib) exposure is estimated as 1318 subject years as of September 2007. Following a review of safety data from the TYVERB (lapatinib) program, GlaxoSmithKline (GSK) would like to advise you that:

- A crude incidence of 0.4% was reported for hepatotoxicity (predominantly transaminase elevations) in the entire TYVERB (lapatinib) clinical trial program. Additionally, TYVERB (lapatinib) is now approved for marketing in over 20 countries and 7 events of hepatotoxicity (predominantly transaminase elevations) have been reported from spontaneous sources.
- Rarely, hepatotoxicity has been severe.
- In the majority of cases patients have recovered when TYVERB (lapatinib) use was discontinued.
- There have been a small number of liver-related deaths in the TYVERB (lapatinib) clinical trial program. GSK has looked closely at each one of these cases. Because of the patients' medical condition and underlying cancer, including in some cases liver metastases, it is difficult to ascertain what role TYVERB may have played in these cases. GSK will continue to carefully evaluate all liver events from clinical trials and post marketing reports to improve its understanding of TYVERB (lapatinib)'s role in these events.
- Hepatotoxicity has also been reported with other tyrosine kinase inhibitors.
- Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment and at approximately monthly intervals thereafter, or as clinically indicated.
- TYVERB (lapatinib) dosing should be discontinued if changes in liver function are severe and treatment with TYVERB (lapatinib) should not be restarted.
- Considering the rare frequency and reversibility of TYVERB (lapatinib) related hepatotoxicity and its use with cancer patients, GSK believes that the risk/benefit of TYVERB (lapatinib) supports its continued use in the metastatic setting.
- In countries where TYVERB (lapatinib) is authorized for marketing GSK intends to update the prescribing information for TYVERB (lapatinib) to include hepatotoxicity. This information will be provided once it has been agreed to with regulatory authorities.

Action Being Taken by GSK

The following actions will be taken by GSK:

- In countries where TYVERB (lapatinib) is authorized for marketing GSK will propose an amendment to Warnings and Precautions section of the TYVERB (lapatinib) prescribing information to include hepatotoxicity and monitoring recommendations. This information will be provided once it has been agreed to with regulatory authorities.
- Additional analyses of data from the TYVERB (lapatinib) clinical program are ongoing.

Healthcare Professionals Please take the following actions:

- Share this information with your patient's other Healthcare Professionals if applicable e.g. family doctor.
- TYVERB (lapatinib)dosing should be discontinued for patients with severe changes in liver function and treatment with TYVERB (lapatinib) should not be restarted.
- Monitor liver function before initiation of treatment, and at approximately monthly intervals thereafter, or as clinically indicated.

The safety of patients is of the utmost importance to GSK and we take a proactive approach to safety monitoring. This includes regular reviews of safety data from clinical studies and post marketing reports.

GSK will keep you informed of relevant developments in a timely manner.

Further Information

In the European Union, TYVERB (lapatinib) was given a positive opinion by the CHMP in December 2007 for grant of a conditional marketing authorisation. Issue of the formal approval by the European Commission is pending.

For further information please contact

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Sincerely,

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