

GLAXOSMITHKLINE SAFETY ADVISORY

Date: 11 March 2008

Dear Healthcare Professional,

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

Key Messages

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

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

As of 05 December 2007, approximately 8702 subjects were estimated to have received TYKERB/TYVERB in clinical trials. Since marketing approval, TYKERB/TYVERB exposure is estimated as 1318 subject years as of September 2007. Following a review of safety data from the TYKERB/TYVERB 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 TYKERB/TYVERB clinical trial program. Additionally, TYKERB/TYVERB 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 TYKERB/TYVERB use was discontinued.
- There have been a small number of liver-related deaths in the TYKERB/TYVERB 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 TYKERB/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 TYKERB/TYVERB's role in these events.
- Hepatotoxicity has also been reported with other tyrosine kinase inhibitors.

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- Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment and at approximately monthly intervals thereafter, or as clinically indicated.
- TYKERB/TYVERB dosing should be discontinued if changes in liver function are severe and treatment with TYKERB/TYVERB should not be restarted.
- Considering the rare frequency and reversibility of TYKERB/TYVERB related hepatotoxicity and its use with cancer patients, GSK believes that the risk/benefit of TYKERB/TYVERB supports its continued use in the metastatic setting.
- In countries where TYKERB/TYVERB is authorized for marketing GSK intends to update the prescribing information for TYKERB/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 TYKERB/TYVERB is authorized for marketing GSK will propose an amendment to Warnings and Precautions section of the TYKERB/TYVERB 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 TYKERB/TYVERB 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.
- TYKERB/TYVERB dosing should be discontinued for patients with severe changes in liver function and treatment with TYKERB/TYVERB should not be restarted.
- Recommend monitoring of 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.

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

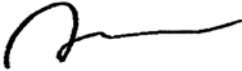
Further Information

In the European Union, lapatinib (TYVERB) 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. Approval by the Norwegian Medicines Agency will follow upon approval by the European Commission.

If you have any questions, please contact

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Sincerely,



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