

**Health Canada Endorsed Important Information on
TYKERB® (lapatinib ditosylate)**



March 20, 2013

Dear Healthcare Professional:

Subject: Updated Information on Efficacy – TYKERB® (lapatinib ditosylate)-based regimens are less effective than HERCEPTIN® (trastuzumab)-based regimens in certain settings

GlaxoSmithKline Inc., in consultation with Health Canada, would like to inform you of important study results concerning the efficacy of TYKERB®. Recently, there have been results reported from two comparative studies of TYKERB® in combination with chemotherapy versus HERCEPTIN® (trastuzumab) in combination with chemotherapy in HER2+ metastatic breast cancer patients:

- EGF111438/CEREBEL, lapatinib/capecitabine versus trastuzumab/capecitabine in HER2+ metastatic breast cancer patients who have progressed on anthracyclines or taxanes
- EGF108919/COMPLETE, lapatinib/taxanes (paclitaxel or docetaxel) versus trastuzumab/taxane in 1st Line HER2+ metastatic breast cancer.

Based on the results of preplanned interim analyses of these two studies, GlaxoSmithKline would like to advise you of the following:

- In patients with HER2+ metastatic breast cancer who have not received prior trastuzumab, comparative data have shown that lapatinib-based regimens are less effective than trastuzumab based treatment regimens.
- Prescribers are reminded that TYKERB® should not be prescribed in combination with capecitabine unless patients have progressed on prior trastuzumab therapy in the metastatic setting.
- GlaxoSmithKline has updated the TYKERB® Product Monograph to include a statement that lapatinib-based regimens are less effective than trastuzumab-based regimens in certain settings.

CEREBEL(EGF111438) (N=540) is a randomised Phase III study comparing the effect of lapatinib in combination with capecitabine relative to trastuzumab in combination with capecitabine on the incidence of CNS as site of first relapse in women with HER2 positive metastatic breast cancer. Patients were stratified based on prior trastuzumab treatment (yes versus no) and number of prior treatments for metastatic disease (0 versus ≥ 1 line). The study was stopped early due to results of a pre-planned interim analysis (N=475). There was superior efficacy with the trastuzumab plus capecitabine combination in terms of progression-free survival (PFS) and overall survival (OS) compared to the lapatinib plus capecitabine combination. Median PFS was 6.60 months in the lapatinib-containing arm compared with 8.05 months in the trastuzumab-containing arm (HR=1.30; 95%CI 1.04 to 1.64). The median OS was 22.7 months in the lapatinib-containing arm compared with 27.3 months in the trastuzumab-containing arm (HR=1.34 (95%CI: 0.95 to 1.90).

COMPLETE is a randomised Phase III study (EGF108919) (N=636) comparing the activity of lapatinib plus taxane followed by lapatinib alone versus trastuzumab plus taxane followed by trastuzumab alone as first line therapy for women with HER2 positive metastatic breast cancer. The study was stopped early due to superior efficacy of the trastuzumab plus taxane combination in terms of progression-free survival. Results from a pre-planned interim analysis showed that the PFS in the lapatinib-containing arm was lower than in the trastuzumab-containing arm (median PFS was 8.8 months in the lapatinib-containing arm compared with 11.4 months in the trastuzumab-containing arm; HR=1.33; 95% CI 1.06 to 1.67, p=0.01). The hazard ratio for OS was 1.1 (95% CI 0.75 to 1.61; p=0.62), based on 18% (n=115) deaths.

Although no new safety information or changes in the established safety profile of lapatinib for the market authorized indications has been reported as a result of these analyses, the Canadian Product Monograph was recently revised to provide more comprehensive guidance on the successful management of lapatinib associated diarrhea, and to highlight the association between lapatinib-induced ALT elevation and severe liver injury with the highly correlated HLA alleles DQA*02:01 and DRB1*07:01.

The revised Product Monograph for TYKERB® 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 TYKERB® should be reported to GlaxoSmithKline or Health Canada.

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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 Health Products Directorate
E-mail: mhpd_dpssc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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

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.

TYKERB® is a registered trademark, used under license by GlaxoSmithKline Inc.

References:

Gelmon KA, Boyle F, Kaufman B, et al. Open-label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2+ metastatic breast cancer: Interim analysis (IA) of NCIC CTG MA.31/GSK EGF 108919. J Clin Oncol. 2012;30(suppl; abstr LBA671).

X Pivot, V Semiglazov, B Zurawsky, R Allerton, A Fabi, E Ciruelos, R Parikh, M DeSilvio, S Santillana and R Swaby : [CEREBEL (EGF111438): An open label randomized phase III study comparing the incidence of CNS metastases in patients(pts) with HER2+ Metastatic Breast Cancer (MBC), treated with Lapatinib plus Capecitabine (LC) versus Trastuzumab plus Capecitabine (TC). Ann Oncol (2012) 23(suppl 9): ix5 abstract LBA11 doi:10.1093/annonc/mds499