Lapatinib Plus Capecitabine For Treating HER-2-POSITIVE METASTATIC BREAST CANCER IN Egyptian Women

Health Technology Appraisal

Issued: May 2014

- **بيانات المستحضر محل الدراسة:**

Intervention	Lapatinib Plus Capecitabine
Trade name	Tykerb
Company name	Gsk
Comparator	Capecitabine

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضر **Lapatinib** في علاج مرضي سرطان الثدي من نوع HER2 Positive . وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية وفي ضوء الممارسة الإكلينيكية.

- **توصية لجنة اقتصاديات الدواء:**

بناء علي طلب الادارة الفنية لمناقصات الادوية والتوصية بعمل دراسة "Pharmacoeconomics" لبيان الجدوى الاقتصادية "CEA" لمستحضر Tykerb Tablet . وبناءً على رأي اساتذة وخبراء الاورام الذين افادوا بان البروتوكول العلاجي Tykerb + Xeloda له فائدة علاجية تفوق استخدام علاج Xeloda فقط في علاج اورام الثدي من نوع HER2 Positive في حالة فشل علاج ال Herceptin وخاصة في حالات ال Metastatic Brain .

ولكن بناءً على السعر المقترح من الشركة فقد تبين من الدراسة الاقتصادية التي قامت بها الوحدة، ان البروتوكول العلاجي Tykerb + Xeloda ليس الأكفأ من حيث الفعالية مقابل التكلفة. ولذا توصي لجنة اقتصاديات الدواء بالتفاوض مع الشركة على السعر او عمل Risk sharing agreement.

علما ان الدراسة التي قامت باجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضرات والتي تم تجميعها من تسعيرة الادارة الفنية لمناقصات الادوية ومناقصات هيئة التأمين الصحي، بالاضافة إلى باقي التكلفة المرتبطة بالإقامة بالمستشفى والأدوية والتبعات المحتملة عن استخدام كل بروتوكول على حدة، وطبقا لتسعيرة نفقة الدولة. كما تم تجميع البيانات الخاصة بالقيمة العلاجية الناتجة عن جودة الحياة المعيشية للمريض ونسبة الحالات المستجيبة للعلاج بالإضافة الى Survival data من الدراسات المنشورة عالميًا.

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English Summary:

ECONOMIC EVALUATION OF LAPATINIB IN HER-2-POSITIVE METASTATIC BREAST CANCER PATIENTS IN EGYPT

- **Introduction**

Breast cancer (BC) is the world's most common cancer among women, and the most likely cause of death from cancer worldwide.[1] The overexpression of Human Epidermal growth factor Receptor 2 (HER2-positive), a protein causing higher tumor aggressiveness and risk of developing metastases, has been found in about 20–30% of breast cancers.[2] Several chemotherapy regimens are recommended for the treatment of HER2-positive Metastatic breast cancer[3].

Trastuzumab, a monoclonal antibody administered by intravenous route, is approved to be used as first-line treatment of HER2+ MBC in patients who have received one or more chemotherapy regimens for metastatic disease.[4] However, many patients do not respond to trastuzumab, less than 35% of patients with HER2+ MBC initially respond to trastuzumab which means that 65% of patients are "primarily" or "inherently" resistant to the drug. On the other hand, about 70% of patients who initially responded experience progression to metastatic disease within a year, suggesting that "secondary" or "acquired" resistance to trastuzumab frequently develops. This highlights the need for newer agents that can be used to treat individuals whose disease has progressed after trastuzumab resistance.[2]

Lapatinib, an orally administered small molecule inhibitor of the tyrosine kinase domains of HER-1 and HER-2 and epidermal growth factor receptor, has been approved by Food and Drug Administration to be used in combination with capecitabine for treatment of HER-2+ MBC (second-line therapy) for those who had been previously treated with trastuzumab.[5] The EGF1000151 clinical trial demonstrated that the addition of lapatinib to capecitabine in the treatment of HER-2+ advanced breast cancer significantly improved the median time to progression (TTP) by 8.5 weeks (18.6 weeks vs 27.1 weeks; P = .00013) and overall response rate by 9.8% (13.9% vs 23.7%; odds ratio = 1.9; 95% confidence interval, 1.1-3.4).[6,7,8]

As we have limited resources to PTES (Pay-at-The-Expense-of-the-State), an Egyptian healthcare payer for patients who doesn't have an insurance coverage, we should only reimburse the cost effective drugs to better allocate our resources. The study was primarily conducted to assess the cost-effectiveness of lapatinib/capecitabine combination from the Egyptian healthcare payer perspective (PTES).

- **Objective**

The objective of the current study was to assess the cost-effectiveness of lapatinib plus capecitabine versus capecitabine alone in human epidermal growth factor receptor-2-positive metastatic breast cancer patients from the Egyptian healthcare payer perspective over a time horizon of ten years.

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- **Economic evaluation Key Features:** [9]

Key Features:	
year of the document	May 2014
Affiliation of authors	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
Purpose of the document	To assess the cost-effectiveness of lapatinib plus capecitabine versus capecitabine alone in human epidermal growth factor receptor-2-positive metastatic breast cancer patients from the Egyptian healthcare payer perspective over a time horizon of ten years
Standard reporting format included	yes
Disclosure	yes
Target audience of funding/ author's interests	Public
Perspective	Health care system
Indication	Human epidermal growth factor receptor-2-positive metastatic breast cancer in Women
Target population	Both those who are uninsured by the Egyptian health care system.
Subgroup analysis	No subgroup analysis
Choice of comparator	Capecitabine is the routinely used intervention for this indication in such patients.
Time horizon	over a ten-year period
Assumptions required	yes
Analytical technique	Cost-effectiveness analysis
Costs to be included	Direct medical costs include costs of treatment and managing strategies according to the Egyptian current practice.
Source of costs	Official sources of unit cost data for products (Tender lists)
Modeling	Markov model
Systematic review of evidences	yes
Preference for effectiveness over efficacy	yes
Outcome measure	The outcomes of the two treatments were measured in terms of quality-adjusted life-years (QALYs)
Method to derive utility	The direct use of EQ-5D
Equity issues stated	All lives, life years, or QALYs are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population

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Discounting costs	A discount rate of 3.5 % per year is used for costs.
Discounting outcomes	A discount rate of 3.5 % per year is used for outcomes.
Sensitivity analysis-parameters	Critical component(s) in the calculation is varied through a relevant range or from worst case to best case scenario.
Sensitivity analysis-methods	One-way sensitivity analysis is performed.
Presenting results	The addition of lapatinib to capecitabine is not clearly cost-effective; and most likely to result in an ICER higher than the threshold limit.
Incremental analysis	yes
Total costs vs. effectiveness (cost/effectiveness ratio)	yes
Portability of results (Generalizability)	The generalizability and extent to which the clinical efficacy data and the economic data are representative is identified and discussed.

Committee Discussion

The main objective of this study was to evaluate the cost-effectiveness of lapatinib plus capecitabine versus capecitabine alone in human epidermal growth factor receptor-2-positive metastatic breast cancer patients. The present study comprised of 3 health states, based on effectiveness data derived from 2 clinical trials[7,8]. In the first trial, 399 patients were randomized, and nine were being screened and were offered combination treatment. In total, 207 and 201 patients were enrolled to combination therapy and monotherapy, respectively. Thirty-six patients receiving monotherapy crossed over to combination therapy following enrollment termination. The median overall survival times were 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.71–1.08; p = .210).[7]With an updated efficacy and biomarker analyses of the first trial, the second trial was a 2 year follow-up for the first trial and showed that the addition of lapatinib to capecitabine provides superior efficacy for women with HER2-positive, advanced breast cancer progressing after treatment with anthracycline-, taxane-, and trastuzumab-based therapy. The addition of lapatinib prolonged TTP with a hazard ratio (HR) of 0.57 (95% CI, 0.43-0.77; P < 0.001) and provided a trend toward improved overall survival (HR: 0.78, 95% CI: 0.55-1.12, P = 0.177), and fewer cases with CNS involvement at first progression (4 vs. 13, P = 0.045). [8]

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This study indicated that the addition of lapatinib to capecitapine was not cost effective when compared with capecitapine alone based on commonly accepted willingness to pay threshold in Egypt. The incremental positive effect was 5.7 quality adjusted life years (QALY) and the incremental cost-effectiveness ratio (ICER) was EGP 277,169 /QALY gained.

While the National Institute of Care Excellence (NICE) uses a threshold of £ 30,000 per QALY [10], the Egyptian threshold value still uncertain to conclude whether the new intervention is cost effective against current intervention or not. World Health Organization proposed many approaches to approximate this threshold. The most common approach is based on gross domestic product (GDP) per capita, where an intervention that, per disability-adjusted life-year (DALY) avoided, costs less than three times the national annual GDP per capita is considered cost–effective.[11] Based on WHO recommendation, the calculated threshold was about EGP 75,000 for 2013.[12]

Data on the costs of breast cancer-related health care services were obtained from a variety of secondary sources. Direct nonmedical costs and indirect costs were not collected in this study.

One of the limitations that should be mentioned in this study, the number of patients in the combination-therapy group who had symptomatic CNS progression was significantly lower than patients in the monotherapy group. Although this subgroup of high-risk patients would benefit most, we couldn't conduct a subgroup analysis because of lack of data on costs and utility of such group at the time of the study.

Similar studies of lapatinib plus capecitabine showed the same conclusion of the present study. Quang et al[13] conducted a cost effectiveness analysis compared lapatinib plus capecitabine versus capecitapine in HER-2–Positive Advanced Breast Cancer which resulted in an additional US$19,630 with an expected gain of 0.12 QALY and an ICER of US$166,113 per QALY gained. As the ICER is higher than the commonly accepted willingness to pay threshold, the addition of lapatinib to capecitabine is not cost-effective.

- **Conclusion**

The economic evaluation of lapatinib plus capecitabine as combination therapy resulted in additional cost of EGP 1,597,796, with an incremental positive effect of 5.7 quality adjusted life years (QALY) or an incremental cost-effectiveness ratio (ICER) of EGP 277,169 /QALY gained. The overall survival of the two arms was found to have the greatest impact on the results.

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Compared with the willingness-to-pay threshold stated by world health organization for lower and middle income countries, the addition of lapatinib to capecitabine is not cost-effective; and most likely to result in an ICER higher than the threshold limit.

- **Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

- **Appraisal Committee members**

Each technology appraisal is appraised by the PE Committee, which is one of CAPA's standing advisory committees and consist of members who represent different specialties such as statistics, clinical evidence, economics, medicine, clinical pharmacy and pharmacoeconomics. A list of the Committee members who took part in the discussions for this appraisal appears below:

- **Dr. Randa El-Dessoki**, Scientific director of global initiatives of the Organization of the economics of medicine management and research outputs.
- **Dr. Mahmoud El-Mahdawy**, General director of Hospital pharmacy administration, Central Administration for Pharmaceutical Affairs, Ministry of Health.
- **Dr. Gihan Hamdy,** Head of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.
- **Dr. Abd Allah Mohammed**, Expert at National Authority for the control of Biopharmaceuticals.
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- **PEU project team**

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