Everolimus Plus Exemestane For Treating Metastatic Breast Cancer In Egyptian Patients

Health Technology Appraisal

Issued: January 2014

- **بيانات المستحضر محل الدراسة:**

Intervention	Everolimus
Trade name	Affinitor
Company name	Novartis
Comparator	Gemcitabine Plus Paclitaxel And Capecitabine Plus Docetaxel

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضر **Everolimus** في علاج مرضي أورام الثدى. وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية العالمية وفي ضوء الممارسة الإكلينيكية المحلية.

- **توصية لجنة اقتصاديات الدواء:**

بناء علي طلب اللجنة العليا لمناقصات الادوية بعمل دراسة جدوى أقتصادية بخصوص مستحضر Affinitor لادراجه ضمن بروتوكولات العلاج على نفقة الدولة. فقد قامت وحدة أقتصاديات الدواء بعمل دراسة اقتصادية لتحليل الاثار المترتبة على ميزانية نفقة الدولة بعد ٣ سنوات لدخول مستحضرAffinitor ضمن بروتوكولات علاج أورام الثدى مقارنة بـ البرتوكول العلاجي الأول وهو emcitabine+paclitaxel والبرتوكول العلاجي الثاني .Capecitabine+docetaxil

وأسفرت النتائج عن ان مستحضر الـ Affinitor يؤثر على ميزانية نفقة الدولة بنسبة ضئيلة تساوي ٠.٢٢ جنيه مصري للمريض الواحد شهريا للسنة الأولي، و٠.٨٣ جنيه مصري للسنة الثانية، و ١.٨٦ جنيه مصري للسنة الثالثة وذلك عند مقارنته كبديل لأستخدام البروتوكول العلاجي Gemcitabine+paclitaxel. حيث ان التكلفة الإجمالية للمريض الواحد شهريا ٢.٩٢ جنيه مصري بعد ثلاثة سنوات.

ـ كما أسفرت الدراسة أيضا عن ان مستحضر الـ Affinitor يؤثر على ميزانية نفقة الدولة بنسبة ضئيلة تساوي ٠.٣٠ جنيه مصري للمريض الواحد شهريا للسنة الأولي، و٠.٤٣ جنيه مصري للسنة الثانية، و ٠.٩٧ جنيه مصري للسنة الثالثة وذلك عند مقارنته كبديل لأستخدام البروتوكول العلاجي Capecitabine+docetaxil. حيث ان التكلفة الإجمالية للمريض الواحد شهريا ١.٥٤ جنيه مصري بعد ثلاثة سنوات.

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- علما ان الدراسة التي قامت باجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضر التي تم تجميعها من تسعيرة نفقة الدولة بالاضافة إلى باقي التكلفة المرتبطة بالإقامة بالمستشفى والأدوية والتبعات المحتملة عن علاج الاثار الجانبية لاستخدام كل بروتوكول على حدة، وطبقا لأسعاروزارة الصحة مع الاخذ فى الاعتبار الحالات الجديدة التى يتم علاجها شهريا ونسبة الفئة المستهدفة

(Target population after Letrozole failure) ونسبة (Market share) لمستحضر Affinitor .

- كما تم تجميع البيانات الخاصة بالقيمة العلاجية (progression free survival - over all survival) ونسبة حدوث الاثار الجانبية المحتملة من استخدام كل بروتوكول من الدراسات المنشورة عالميًا والتي تقدم أعلى مستوى من صدق الدليل العلمي Randomized trials & BOLERO 2 .

English Summary:

Budget Impact Analysis Of Everolimus Plus Exemestane Versus Gemcitabine Plus Paclitaxel And Capecitabine Plus Docetaxel In Metastatic Breast Cancer Patients In Egypt

- **Introduction**

Breast Cancer is the most common malignancy among women in most developed and developing regions of the world with nearly a million new cases each year. It accounts for nearly 21% of all cancers among women worldwide. The distribution of breast cancer within developing countries shows a higher incidence of breast cancer in urban than in rural areas. In Egypt, as in many other parts of the world, breast cancer is the most common type of cancer: it accounts for approximately 38% of reported malignancies among Egyptian women [1].

Approximately 58% of patients with breast cancer are classified as having hormone receptor positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) disease. Current treatment guidelines for HR+, HER2- advanced breast cancer (ABC) recommend treatments based on individual patient characteristics, and hormone therapy is the commonly recommended initial treatment for postmenopausal women.

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Hormone therapy with aromatase inhibitors (e.g., letrozole and anastrozole) is the mainstay of initial treatment; however, not all patients respond to the initial hormonal treatment, and most patients who respond initially will later develop resistance and experience disease progression. Patients experiencing progression after initial treatment with an aromatase inhibitor may be treated with another aromatase inhibitor (e.g., exemestane) or with an estrogen-receptor antagonist (e.g., tamoxifen or fulvestrant).

Everolimus, in combination with exemestane, has recently been approved for the treatment of advanced HR+, HER2- breast cancer in post-menopausal women after they fail treatment with letrozole or anastrozole. Everolimus targets the mammalian target of rapamycin (mTOR) pathway in cancer cells. The approval is based on the phase III randomized clinical trial, BOLERO-2, which has compared the safety and efficacy of everolimus in combination with exemestane to exemestane alone for the treatment of HR, HER2-ABC in post-menopausal women following failure with letrozole or anastrozole. Compared to exemestane alone, combination therapy of everolimus and exemestane was associated with significantly longer progression-free survival (PFS) in the study population. The superior efficacy, measured by PFS, of everolimus plus exemestane was consistent across all sub-groups evaluated in the clinical trial, e.g., patients who had previously taken multiple prior therapies, patients 65 or older, and patients with metastatic disease. These findings indicate the potential for everolimus to enhance the clinical benefit of hormonal therapy in refractory HR+, HER2- ABC patients. However, in light of healthcare resource constraints, it's crucial to get information about the expected budgetary impact of new treatments, such as everolimus, to guide decisions about coverage and reimbursement issues [2]. Current treatment options in Egypt include two chemotherapeutic regimens (gemcitabine plus paclitaxel or capecitabine plus docetaxel). The objective of this study was to compare between the budget impacts of introducing everolimus plus exemestane as the alternative treatment option after letrozole or anastrozole failure versus the two traditional regimens used in post-menopausal women with HR+, HER2- ABC.

- **Objective**

To estimate the budget impact of everolimus-exemestane versus the most commonly used regimens in the Egyptian practice; gemcitabine-paclitaxel and capecitabine-docetaxel for a health care plan that introduces

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everolimus for post-menopausal hormone receptor positive, human epidermal growth factor receptor-2 negative metastatic breast cancer (HR+,HER2-MBC) patients over three years.

- **Economic evaluation Key Features:** [3]

Key features:	
Year of the document	January 2014
Affiliation of authors	Pharmacoeconomic unit, central administration for pharmaceutical affairs
Purpose of the document	Conduct Budget impact analysis of everolimus plus exemestane versus gemcitabine plus paclitaxel and capecitabine plus docetaxel in metastatic breast cancer patients in egypt
Standard reporting format included	Yes
Disclosure	Yes
Target audience of funding/ author's interests	Public, healthcare industries and clinicians
Perspective	The insurer perspective
Indication	Treatment of breast cancer
Target population	Those who are insured by the egyptian health care system.
Subgroup analysis	Only for those whom clinical and cost effectiveness may be expected to differ from that of the overall population.
Choice of comparator	Gemcitabine plus paclitaxel and capecitabine plus docetaxel
Time horizon	Over a three-year period
Assumptions required	Yes
Analytical technique	Budget impact analysis
Costs to be included	Total costs include costs of treatment and managing strategies according to the egyptian current practice.

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Source of costs	Official sources of unit cost data for products (e.g. 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 (QALY)
Method to derive utility	No utility is derived
Equity issues stated	All lives, life years are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population
Discounting costs	A discount rate of 3.5 % per year is used for costs and outcomes.
Discounting outcomes	A discount rate of 3.5 % per year is used for costs and outcomes.
Sensitivity analysis-parameters and range	Critical component(s) in the calculation is varied through a relevant range or from worst case to best case.
Sensitivity analysis-methods	One-way sensitivity analysis is performed.
Presenting results	Increased acquisition costs of everolimus-exemestane for HR+,HER2-MBC treatment are expected to be obviously offset by both the reduced number of progressed patients and the relatively small medical costs
Incremental analysis	Yes
Total costs vs. Effectiveness (cost/effectiveness ratio)	NA

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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**

Commonly recommended treatment options for postmenopausal women with HR+, HER2- ABC include hormone therapy with anti-estrogens (tamoxifen, fulvestrant) and the third-generation aromatase inhibitors (letrozole, anastrozole, and exemestane). However, there are substantial unmet needs in this population, especially after primary non-response or disease relapse with letrozole or anastrozole treatment [4]. The recent BOLERO-2 trial showed that the combination of everolimus with exemestane significantly prolonged PFS compared to exemestane alone (7.8 months vs 3.2 months) among post-menopausal women with HR+, HER2- ABC after letrozole or anastrozole failure [5], making everolimus plus exemestane a promising treatment option for this patient population. Yet, because everolimus is associated with higher drug acquisition costs compared to alternatives, such as exemestane monotherapy or tamoxifen, for which generic drugs are available, the economic impact of including everolimus as a new treatment option would be of interest to payers.

The present study sought to evaluate the budget impact of adding everolimus to a health plan formulary for this indication at the first three years. Budget impact analysis has become increasingly important to the comprehensive economic assessment of new pharmaceutical products. The estimated impact of a newly-available drug on annual pharmacy and medical expenditures is crucial not only for financial planning, but also for anticipating its effect on the public health and service provision within the healthcare system [6].

The model accounted for the potential entry of everolimus as a treatment option after letrozole or anastrozole failure. Adding it, is projected to have a limited impact on the total budget (LE 0.98 & LE 1.86 PMPM in year 3 against Capecitabine/Docetaxel & Gemcitabine/Paclitaxel respectively). Results remained robust to some extent, although, in its one-way sensitivity analysis, they were so sensitive to the reimbursement cost of everolimus (in case of Capecitabine/Docetaxel scenario), an issue stimulating the need for proper

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negotiating on its reimbursed price. Whereas, in case of Gemcitabine/Paclitaxel, the analysis proved its sensitivity towards the number of eligible patients, and the acquisition costs for the two alternatives. Overall, the low estimated impact of everolimus/exemestane entry on total plan budget and large potential gains in PFS from everolimus plus exemestane combination therapy support the formulary placement of everolimus for post-menopausal women with HR+, HER2- ABC who have failed letrozole or anastrozole.

As with most economic models, results from this budget impact analysis are contingent on the assumptions that were applied. While every effort was made to obtain key model inputs from the best available evidence, assumptions about some parameters were necessary for the budget impact estimation and may impact the model output. First, due to limited real-world data on treatment patterns and outcomes in HR+, HER2- ABC, published data from clinical trials were used to estimate the prevalence of letrozole- or anastrozole-refractory disease, as well as the percentages of these individuals who would require a treatment option after letrozole or anastrozole failure within a given year.

The model estimates should be validated or refined as additional data from real-world clinical practice become available. Second, median PFS for each drug, which is used as a proxy for mean duration on medication, was obtained from separate clinical trials. Although these studies had similar eligibility criteria, heterogeneity across the trial populations may still exist, which may affect the PFS estimates associated with different treatments. Lastly, the study is in a great need for precise and up-to-date Egyptian epidemiological data to rely on. Overall, the model could be further updated as additional clinical data are available.

- **Conclusion**

Increased acquisition costs of everolimus-exemestane for HR+HER2-MBC treatment are expected to be obviously offset by both the reduced number of progressed patients and the relatively small medical costs due to avoided adverse events of each of gemcitabine-paclitaxel and capecitabine-docetaxel regimens. The expected budget impact of covering everolimus for this group of patients was relatively small.

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- **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:

- **Prof. Tarek Hashim**, Professor of oncology, Faculty of Medicine, Monofeya university.
- **Prof. Khalid Samak,** Deputy Head of the Secretariat of medical centers specialized oncology
- **Prof. Mohsen Barsoum**, Professor of oncology, The National Institute of Oncology.
- **Prof. Hesham Tawfiq**, Assistant professor of Oncology, Faculty of Medicine, Tanta University
- **Prof. Mohammad Abdullah**, Professor of oncology, Faculty of Medicine, Cairo university
- **Prof. Ebtisam Saad Eddin,** Professor Of Oncology, Faculty of Medicine, Cairo university**.**
- **Prof. Emad Hamada**, Professor Of Oncology, Faculty of Medicine, Cairo university**.**
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- **Prof. Ahmed Hassouna**, Consultant of clinical trials.
- **Prof. Randa El-Dessouki,** Scientific director of global initiatives of the Organization of the economics of medicine management and research outputs.
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- **PEU project team**
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