Denosumab versus zoledronic acid in breast & prostate cancer patients with bone metastasis

Health Technology Appraisal

Issued: september 2016

- **بيانات المستحضر محل الدراسة:**

Intervention	Denosumab
Trade name	Xgeva
Company name	Amgen
Comparator	Zoledronic acid

- **تاريخ عرض المستحضر:**

تم تحويل المستحضر من الإجتماع المنعقد مع قطاعات الصيدلة التابعة لوزارة الصحة بتاريخ ٢٠١٦/٦/٢٩ إلي وحدة إقتصاديات الدواء لإجراء دراسة جدوي إقتصادية تقارن كلا المستحضرين zoledronic acid &denosumab في علاج solid tumors with bone metastasis

- **الهدف:**

- تقييم الفعالية لقاء التكلفة لمستحضر **denosumab** مقارنه بمستحضر **zoledronic acid** في علاج مرض النقائل العظمية المصاحبه لسرطان الثدي والبروستاتا وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية العالمية وفي ضوء الممارسة الإكلينيكية المحلية.

- علما ان الدراسة التي قامت باجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضرات والتي تم تجميعها من تسعيرة الادارة الفنية لمناقصات الادوية ومناقصات مستشفيات وزاره الصحة ، بالاضافة إلى باقي التكلفة المرتبطة بالإقامة بالمستشفى والأدوية والتبعات المحتملة عن علاج حالات الكسر بأنواعها والناتجة عن استخدام كل بروتوكول على حدة، وطبقا لتسعيرة نفقة الدولة .

- تم تجميع البيانات الخاصة بالقيمة العلاجية الناتجة عن جودة الحياة المعيشية للمريض "utility" ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالميًا .

قرار اللجنة:

في ضوء متابعة إجراء دراسة جدوي إقتصادية (cost effectiveness study) لتحديد القيمة العلاجية المضافة مقابل التكلفة للمستحضرات.

تم مراجعة النتائج النهائية للدراسات ومن يترتب عليها من قرارات وذلك بحضور المتخصصيين في مجال الاقتصاد وتقييم الدليل العلمي والاحصاء للإفادة بصلاحيتها Validation من ناحية الجودة العلمية في منهج الدراسة والتحليل الإحصائي المتبع.

أظهرت النتائج ان مستحضر Denosumab عند سعر ٢٤٠٠ جنيه ليس هو الأكفء من حيث الفعالية لقاء التكلفة not cost effective وذلك بالمقارنة بمستحضر Zoledronic acid عند سعر ٩٨٠ جنيه في كلا من مرضي breast and prostate cancer .

وذلك علي الرغم من تفوق مستحضر Denosumab في تحسين جودة الحياة المعيشية، إذ يوجد فرق في التكلفة بين المستحضرين لصالح مستحضر Zoledronic acid الذي يعتبر الأرخص حيث يتم تقليل مرات اعطاءه من كل شهر إلي كل ثلاثة أشهر مع الحفاظ علي نفس الفعالية العلاجية خلال العام الثاني من العلاج.

وبمراجعة قواعد العلاج الاسترشادية في هذا الغرض العلاجي تبين ان نسبة حدوث osteonecrosis of the jaw كأثر جانبي من كلا المستحضرين تزداد بعد سنتين من بدء العلاج لذا يتم إيقافه بعد تلك المدة وعليه تم إجراء الدراسه وحساب التكلفه والفعاليه علي مدار سنتين فقط. .

- كما أنه اخلصت اللجنه إلي قصر إستخدام denosumab لمرضي الكلي حيث يمنع إستخدام zoledronic acid في هذه الفئه من المرضي وذلك لما ينتج عنه من مشاكل وأضرار جانبيه للكلي .

English Summary:

Cost-effectiveness of denosumab versus zoledronic acid in the treatment of breast and prostate cancer Patients with bone metastasis: Adecision tree Model

Introduction:

Patients with advanced solid tumors commonly develop bone metastases. Bone metastases cause bone destruction through increased osteoclast activity, frequently resulting in skeletal complications known as skeletal-related events (SREs; commonly defined as pathologic fracture, radiation to bone, surgery to bone and spinal cord compression). SREs are associated with significant and debilitating pain, impaired morbidity, reduced quality of life, substantial health-resource utilisation and associated costs.

Bisphosphonates are bone targeted agents that have been historically used to reduce the risk of SREs in patients with bone metastases. Zoledronic acid has been considered the standard of care and has been shown to prolong time to first SRE and reduce the number of SREs; however, many patients with bone metastases continue to experience SREs. ZA is infused intravenously (IV) every 3–4 weeks and is associated with renal toxicity **(1).**

Denosumab has a different and novel mode of action; it is the first fully human monoclonal IgG2 antibody that binds to RANK ligand. RANK ligand is an essential mediator of the formation, activation and survival of osteoclasts.

Denosumab (120 mg subcutaneous injection (SC) every 4 weeks) was compared with ZA (4 mg IV every 4 weeks) in three identically designed phase III head to head clinical trials of patients with bone metastases from solid tumours (breast cancer, prostate cancer and other solid tumours or multiple myeloma. .Denosumab does not require renal monitoring. The overall incidence of adverse events was similar between denosumab and Zoledronic acid **(2, 3)**.

Objective:

To evaluate the cost- effectiveness of denosumab versus zoledronic acid in breast and prostate cancer with bone metastasis from health insurance perspective

- **Economic evaluation Key Features (4)**

Key Features:	
year of the document	September 2016
Affiliation of authors	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
Purpose of the document	Evaluation the cost-effectiveness of using denosumab versus zoledronic acid in the treatment of breast and prostate cancer patients with bone metastasis.
Standard reporting format included	yes
Disclosure	yes
Target audience of funding/ author's interests	Public and private payers, healthcare industries and clinicians
Perspective	Ministry of health perspective
Indication	Treatment of breast and prostate cancer with bone metastasis.
Target population	Those who insured by the Egyptian health care system
Subgroup analysis	No subgroup analysis was done.
Choice of comparator	Zoledronic acid
Time horizon	Decision tree over one-year as a base case and over 2-years as another scenario representing the clinical practice.
Assumptions required	yes
Analytical technique	Cost-effectiveness analysis

Costs to be included	Total 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 (e.g. Tender lists) and MOH hospitals.
Modeling	Decision tree 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	Utility taken from published study used Time trade off method (TTO) to calculate utility.
Equity issues stated	All lives, life years, or QALYs are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population

Discounting costs	Not applicable.
Discounting outcomes	Not applicable.
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	Denosumab is not cost-effective compared to zoledronic acid in management of breast and prostate cancer patients with bone metastasis.
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 discussed.

Committee Discussion:

Due to the novel mode of action of denosumab and the need for it in patients with renal problems who can't tolerate zoledronic acid , it is important to evaluate its efficacy and impact on the quality of life of the patients. So the main objective of this economic evaluation study is to evaluate the cost effectiveness of denosumab versus zoledronic acid in patients with bone metastasis from breast and prostate cancer.

A comprehensive search of PubMed and MEDLINE was conducted for English articles published to retrieve the available published data regarding Randomized controlled Trials (RCTs), systematic reviews, and meta-analyses of RCTs. because they provide the least biased and most robust evidence regarding

treatment. All indirect clinical trials were excluded; only head to head clinical studies comparing denosumab with zoledronic acid in the target indication are included in the economic study.

The clinical parameters in breast cancer patients were derived from head to head, randomized, double-blind, double-dummy, active controlled study compared denosumab with zoledronic acid for the treatment of bone metastases in breast cancer patients involved 322 centers in Europe, North America, South America, Japan, Australia, India, and South Africa. 2,046 Patients were randomly assigned to receive either a subcutaneous injection of denosumab 120 mg and an intravenous infusion of placebo every 4 weeks or an intravenous infusion (lasting no less than 15 minutes) of zoledronic acid 4 mg and a subcutaneous injection of placebo every 4 weeks. The primary end point was time to first on-study skeletal-related event (non-inferiority test**).** **[5]** , The clinical parameters in prostate cancer patients were derived from a phase 3 randomized multicenter study which enrolled patients from 342 centres in 39 countries worldwide.1904 patients were enrolled in the study of which 951 patients assigned to receive zoledronic acid (I.V) 4mg and 950 patients assigned to receive denosumab (S.C) 120 mg. The primary endpoint was time to first on-study skeletal-related event, and was assessed for non-inferiority**.** **[6]**

Utility values were derived from a previously published clinical study which involved 187 participants of the general population. The draft health states were administered in a TTO interview to ensure that respondents were able to understand the health states and the interview task, a 2-year time frame was used in this study so that the impact of the SREs would be judged within the context of a realistic life expectancy for a patient with advanced cancer and bone metastases **[7]**. Disutility caused by the duration of infusion in case of zoledronic acid and by subcutaneous injection in case of denosumab was taken from another study involved 121 participants from UK and time trade off method was used .**[8]**

Direct medical costs regarding cost of treatment, monitoring test performed and cost of management of side effects were obtained from the Ministry of health hospitals in Egypt.

The results of the cost effectiveness study revealed that denosumab isn't cost effective compared to zoledronic acid in both breast and prostate cancer with bone metastasis with an ICER of 1,423,807 EGP/QALY in breast cancer and an ICER of 1,869,396 EGP/QALY in prostate cancer over a two- year time horizon decision tree model.

This result wasn't comparable with the results of a cost -effectiveness study performed in United States which compared denosumab versus zoledronic acid in bone metastasis from solid tumors. The study conclusion was that denosumab is a cost-effective treatment option for the prevention of SREs in patients with advanced solid tumors and bone metastases compared to ZA. The overall value of denosumab is based on superior efficacy, favorable safety, and more efficient administration. **[9]**
But the result in our model was comparable with an economic evaluation study comparing both interventions in hormone refractory prostate cancer patients with bone metastasis which concluded that

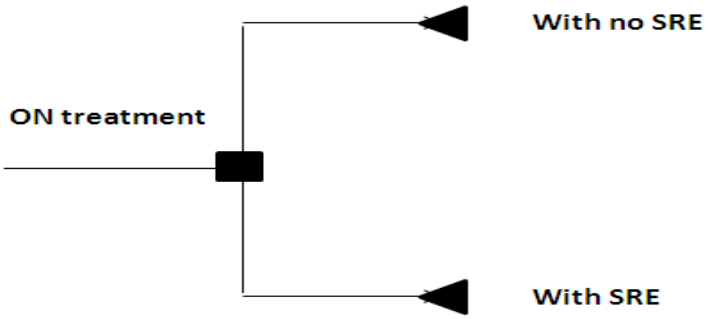
although denosumab has demonstrated benefits over zoledronic acid in preventing or delaying SREs in a phase 3 trial, it may be a costly alternative to zoledronic acid from a U.S. payer perspective **[10].** **And also comparable with another** economic study, comparing the two interventions in breast cancer patients with bone metastasis in United States. It concluded that although denosumab demonstrated superiority in preventing SREs in the phase III trial, it may not be cost-effective compared with zoledronic acid because of its high cost.**[11]**

The limitation of this economic study seems to be represented by short time horizon which is over a 2 years only but according to recently published guidelines and expert opinion the risk of jaw osteonecrosis appears to be related to time on bone-targeted therapy and since it happens treatment should be stopped; therefore caution should be taken in using these agents more than 2 years. And for this reason we measured outcomes and costs in our model over 2-years only. **[12]**

This economic evaluation was a cost-utility assessment that compared projected costs and outcomes of two alternative treatment options on the basis of trial results from healthcare perspective. The cost per QALY is a useful measure, as the ratio is not disease-specific and can be compared across a spectrum of therapeutic interventions. Cost-utility analyses are, thus, the preferred type of economic evaluation and this is the main strength point of the study.

As in all modeling exercises, several assumptions were made in this study leading to uncertainties in the results. In this analysis, we explicitly accounted for these uncertainties by assigning confidence intervals and plausibility ranges based on published sources to the quality-of-life, skeletal related events probabilities, and monitoring costs in the model. Robustness of results was assessed by using sensitivity analysis. One way sensitivity analysis was conducted and illustrated that the key factor which has the greatest impact on the result in breast cancer indication is the 2-year probability of SRE in zoledronic acid arm while the key driver in prostate cancer indication is the cost of denosumab.

Figure 1: illustrating the decision tree model of the cost effectiveness study



SRE: skeletal related events.

- **Conclusion**

It is important to address both the clinical and the economic implications of a new therapy from the payer perspective before deciding on public reimbursement of new therapies. Taking the above-mentioned limitations and uncertainties in consideration the conclusion is that denosumab is not cost-effective versus zoledronic acid in both breast and prostate cancer patients with bone metastasis from Ministry of health perspective.

- **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:

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