

## Zoledronic acid versus pamidronic acid in breast cancer patients with bone metastasis

### Health Technology Appraisal

Issued: October 2015

• بيانات المستحضر محل الدراسة:

Intervention	Zoledronic acid
Trade name	zometa
Company name	Novartis
Comparator	Pamidronic acid

• الهدف:

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

• توصية لجنة اقتصاديات الدواء:

بعد البحث في الدراسات الإكلينيكية التي تقارن كلا المستحضرين تبين عدم وجود فرق ملحوظ في النتائج الأولية للدراسات الإكلينيكية **primary objectives** بين المستحضرين ولوحظ ذلك في جميع الدراسات الإكلينيكية وبالتالي تم الإعتماد فيها علي نتائج ثانوية **secondary outcomes** لبناء دراسة الجدوي الإقتصادية وبعد إجراء الدراسة تبين أن مستحضر **zoledronic acid** هو الأكفأ من حيث الفعالية لقاء التكلفة مقارنة بمستحضر **pamidronic acid** في علاج **breast cancer with bone metastasis** عند قيمة تزايدية تقدر ب ٢٨,٨٥٨ ج.م/QALY والتي تعتبر أقل من الحد المسموح به لقبول المستحضرات من حيث الفعالية لقاء التكلفة والذي يمثل ٣ أضعاف الناتج القومي .

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

- تم تجميع البيانات الخاصة بالقيمة العلاجية الناتجة عن جودة الحياة المعيشية للمريض "QUALITY OF LIFE" ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالمياً .

*English Summary:*

**Cost-effectiveness of zoledronic acid as versus pamidronic acid in the treatment of breast cancer Patients with bone metastasis: Adecision tree Model**

• **Introduction**

Bone metastases are a common cause of skeletal morbidity in patients with advanced breast carcinoma. Among women with advanced metastatic breast carcinoma, approximately 65–75% will develop bone metastases (1). Bone metastases are associated with a variety of skeletal complications, including bone pain, pathologic fractures, spinal cord compression and potentially life-threatening hypercalcemia of malignancy (HCM), which complicate the clinical course and adversely affect quality of life.

Current palliative therapy for patients with bone metastases includes primarily external beam radiotherapy, radionuclides, and bisphosphonates. Bisphosphonates are potent inhibitors of osteoclast mediated bone resorption and have been shown to reduce tumor-induced osteolysis in patients with malignant bone disease. Pamidronate (90 mg as a 2-hour infusion every 3–4 weeks) has been shown to reduce the occurrence and delay the onset of skeletal complications significantly for up to 2 years compared with placebo in patients with breast carcinoma and at least 1 osteolytic bone lesion at study entry, as determined by radiologic appearance (2–3).

Zoledronic acid is a new bisphosphonate that has demonstrated greater potency than pamidronate or other commercially available bisphosphonates in several preclinical models of bone resorption (4). Zoledronic acid also has demonstrated greater clinical activity in the treatment of moderate-to-severe hypercalcemia of malignancy (HCM); a single dose of zoledronic acid (4 mg or 8 mg) was significantly more effective than 90 mg of pamidronate at normalizing corrected serum calcium (5). Although , pamidronate required a lengthy (2-hour or 4-hour) infusion every 3–4 weeks, Zoledronic acid can be administered safely as a 15-minute infusion which is considered one of its benefits over pamidronate and highly affect the utility of the patient.

Zoledronic acid has demonstrated superiority over pamidronate in the treatment of HCM (6) and is the first bisphosphonate to demonstrate efficacy in patients with bone metastases from solid tumors other than breast carcinoma, including prostate carcinoma, non-small cell lung carcinoma, and a variety of other tumor types (7-8). In the international, randomized, comparative study of zoledronic acid versus pamidronate in 1648 patients with advanced breast carcinoma and multiple myeloma, 4 mg of zoledronic acid (as a 15-minute infusion) was as effective as 90 mg of pamidronate (as a 2-hour infusion) in the overall efficacy analysis, with a similar safety profile.(9) This large data base provided the opportunity to examine the clinical benefit of zoledronic acid in various patient subsets. Therefore, an analysis of the breast carcinoma strata (n 1130 patients) was performed, and patients were subdivided based on the radiologic appearance of their bone

metastases (i.e., patients with at least 1 osteolytic lesion or nonlytic lesions at study entry) to determine how zoledronic acid compared with pamidronate in a patient population similar to that of the original placebo-controlled pamidronate studies in patients with breast carcinoma.

- **Objective**

The objective was to evaluate, from the healthcare system perspective, the cost-effectiveness of using zoledronic acid versus pamidronic acid in the treatment of breast cancer patients with bone metastasis.

- **Economic evaluation Key Features: (10)**

<b>Key Features:</b>	
<b>year of the document</b>	October 2015
<b>Affiliation of authors</b>	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
<b>Purpose of the document</b>	Evaluation the cost-effectiveness of using zoledronic acid versus pamidronic acid in the treatment of breast cancer patients with bone metastasis.
<b>Standard reporting format included</b>	yes
<b>Disclosure</b>	yes
<b>Target audience of funding/ author's interests</b>	Public and private payers, healthcare industries and clinicians
<b>Perspective</b>	healthcare perspective
<b>Indication</b>	Treatment of breast cancer with bone metastasis.
<b>Target population</b>	Those who insured by the Egyptian health care system
<b>Subgroup analysis</b>	Only for those whom clinical and cost effectiveness may be expected to differ from that of the overall population.
<b>Choice of comparator</b>	Pamidronic acid
<b>Time horizon</b>	Decision tree over one-year
<b>Assumptions required</b>	yes
<b>Analytical technique</b>	Cost-effectiveness analysis
<b>Costs to be included</b>	Total costs include costs of treatment and managing strategies according to the Egyptian current practice.
<b>Source of costs</b>	Official sources of unit cost data for products (e.g. Tender lists)
<b>Modeling</b>	Decision tree model
<b>Systematic review of evidences</b>	yes
<b>Preference for effectiveness over efficacy</b>	yes
<b>Outcome measure</b>	The outcomes of the two treatments were measured in terms of quality-adjusted life-years (QALYs)
<b>Method to derive utility</b>	Estimated from literature

<b>Equity issues stated</b>	All lives, life years, or QALYs are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population
<b>Discounting costs</b>	Not applicable.
<b>Discounting outcomes</b>	Not applicable.
<b>Sensitivity analysis-parameters and range</b>	Critical component(s) in the calculation is varied through a relevant range or from worst case to best case.
<b>Sensitivity analysis-methods</b>	One-way sensitivity analysis is performed.
<b>Presenting results</b>	Zoledronic acid is cost-effective compared to pamidronic acid in management of breast cancer with bone metastasis.
<b>Incremental analysis</b>	yes
<b>Total costs vs. effectiveness (cost/effectiveness ratio)</b>	yes
<b>Portability of results (Generalizability)</b>	The generalizability and extent to which the clinical efficacy data and the economic data are representative is discussed.

#### • **Committee Discussion**

Bone metastases occur in 65–75% of patients with advanced breast carcinoma, and most bone metastases have an osteolytic appearance on radiographs. (11) Without bisphosphonate therapy, patients with osteolytic lesions from advanced breast carcinoma suffer skeletal complications at an average rate of 3–4 events per year and experience their first pathologic fracture a median of 7 months after the diagnosis of bone metastases. (12) So in this analysis we developed a decision tree model to estimate the incremental cost effectiveness of zoledronic acid versus pamidronate in breast cancer with bone metastasis.

The results of the economic study indicated that zoledronic acid is a cost effective intervention when compared with pamidronic acid (the standard therapy) at an ICER value of 28858 QALY/EGP, which is lower than the maximum accepted threshold of 3 times GDP/Capita as stated by WHO.

The clinical parameters of the model were taken from "Zoledronic Acid is Superior to Pamidronate for the Treatment of Bone Metastases in Breast Carcinoma Patients with at Least One Osteolytic Lesion" trial which enrolled 1130 patients with breast carcinoma who had all types of bone metastases (osteolytic, mixed, or osteoblastic by radiology), the proportion of those who had an skeletal related events (SRE) was the primary endpoint and was comparable between treatment groups, in the model we depend on secondary outcome which is the time to first SRE and was significantly longer in the 4-mg Zol group compared with the Pam group .

Utility values were derived from a previously published clinical study and disutility caused by the duration of infusion was taken into consideration and subtracted from the utility of each health state, so the adjusted utility value is the one which used in the model to calculate QALY which is the final outcome and this is one of the main strength points of the economic study.

Till now there is no head to head cost effectiveness study between zoledronic acid versus pamidronate, the only available cost effectiveness study compared oral ibandronate versus i.v zoledronic acid and i.v pamidronic acid which showed that ibandronate was more cost effective than both zoledronic and pamidronic acids.

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, time to first SRE, and monitoring costs in the model.

One of the limitations of the model is that we depend on secondary outcomes which is an observational data and has a low level of evidence; another limitation is the short time horizon of the study which was over 12 months due to lack of long term efficacy data.

Robustness of results was assessed by using sensitivity analysis. One way sensitivity analysis was conducted and illustrated that the parameter which has the highest impact on the result was the probability of patients with skeletal related events (SRE) in pamidronate arm.

- **Conclusion**

It is important to address both the clinical and the economic implications of a new therapy from the payer perspective before deciding the public reimbursement of new therapies. Taking the above-mentioned limitations and uncertainties in consideration, zoledronic acid is the cost-effective option for management of breast cancer with bone metastasis.

- **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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