Zoledronic Acid For Treating Osteoporosis in postmenopausal Egyptian Patients

Health Technology Appraisal

Issued: July 2014

- **بيانات المستحضر محل الدراسة:**

Intervention	Zoledronic Acid
Trade name	Aclasta
Company name	GSK
Comparator	Alendronic Acid

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضر **Zoledronic Acid** في علاج مرضي هشاشة العظام بعد انقطاع الطمث. 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 الطلب المحول من الإدارة الفنية لمناقصات الادوية بالتوصية بعمل دراسة "Pharmacoeconomics" لمستحضر الAclasta. فقد قامت وحدة اقتصاديات الدواء بعمل "Cost Effectiveness Study" بين مادتي ال(Zoledronic Acid) Aclasta والعلاج التقليدي متمثلاً في ال(Alendronic Acid).

ووجدت الدراسة أن مستحضر ال Aclasta هو الأكفأ من حيث الفعالية مقابل التكلفة، وذلك بعد احتساب نسبة فعالية التكلفة المتزايدة والتي تُقدر بـ345 LE/QALY وهي تعتبر أقل من الحد الأقصي الذي أقرته منظمة الصحة العالمية لاحتساب نسبة فعالية التكلفة المتزايدة للدول النامية ذات الدخل المتوسط (ويساوى ٣ اضعاف ناتج الدخل القومي "GDP").

- 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 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 "QUALITY OF LIFE" ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالميًا .

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English Summary:

Cost-effectiveness of Zoledronic Acid versus Alendronic Acid in the treatment of Osteoporosis in postmenopausal Egyptian Patients: A Markov Model

- **Introduction**

Osteoporosis is a major public health problem leading to an enhanced fragility of the skeleton [1]. It is defined by low Bone Mineral Density (BMD). The major concern with low BMD is the high risk of fractures to non-vertebral bones such as the wrist or to the hip. A hip fracture may require extended hospital stay, surgical repair and rehabilitation therapy, and is associated with increased risk of death [2]. Osteoporosis causes more than 8.9 million fractures annually worldwide [3]. Today, a 50-years old woman is estimated to have a 40% risk of presenting an osteoporotic related fracture at some point in her life [4]. In Egypt, based on different studies, it has been calculated that 53.9% of postmenopausal women have osteopenia, a condition in which bone mineral density is lower than normal, and 28.4% have osteoporosis; in men, 26% have osteopenia and 21.9% have osteoporosis [5,6].

Pharmacologic treatment of osteoporosis consists of antiresorptive drugs that inhibit osteoclastic bone resorption or, anabolic agents. The most commonly prescribed treatments are bisphosphonates, e.g. alendronate, risedronate, etidronate, ibandronate, and the recently developed zoledronic acid. The biggest challenge of these treatment options is the poor long-term patient adherence to the treatment regimen with frequent administration which leads to poor drug effectiveness [7]. One possible way to improve adherence would be to develop treatments which require less frequent dosing schedules. New dosing schedules are recently available, including those that require an annual regimen such as zoledronic acid.

Zoledronic acid 5 mg is infused over a 15-minute period once a year, whereas alendronic acid is given as a once-weekly 70-mg tablet or a once-daily 10-mg tablet, risedronate as a once-daily 5-mg, a once-weekly 35-mg tablet, or a once-monthly 150-mg tablet, and ibandronate as a once-monthly 150-mg tablet or as a 3-mg quarterly injection. Etidronate is licensed at a dose of 400 mg/d for 14 days in a 3-month cycle [4].

- **Objective**

The objective was to evaluate, from the Ministry of Health perspective, the cost-effectiveness of using zoledronic acid 5mg compared to that of alendronic acid in the treatment of osteoporosis in postmenopausal Egyptian patients.

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- **Economic evaluation Key Features:**

Key Features:	
year of the document	July 2014
Affiliation of authors	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
Purpose of the document	Evaluation the cost-effectiveness of using Zoledronic acid 5mg compared to Alendronic acid in the treatment of Osteoporosis in postmenopausal Egyptian patients
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 Osteoporosis in postmenopausal
Target population	Those who 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	Alendronic acid
Time horizon	over a five-year period
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)
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 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	Zoledronic acid is cost-effective alternative to the use of Alendronic acid for management of post-menopausal women with osteoporosis.
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**

It is important to identify the most cost-effective treatment in women with postmenopausal osteoporosis from a range of alternatives. To support reimbursement decision-making in Egypt, Decision analysis is a quantitative method for synthesizing data from numerous sources for the evaluation of treatment alternatives and was developed to determine the cost-effectiveness of the zoledronic acid as compared to, the currently used regimen, alendronic acid.

The results of the model in this study demonstrate that zoledronic acid is cost-effective compared with alendronic acid and should be advocated for patients with postmenopausal osteoporosis. Interestingly, the zoledronic acid group exhibited a small gain in QALYs and costs compared with the alendronic acid group. Thus, the new treatment (Zoledronic acid) is cost-effective because its ICER value is lower than the cost/QALY threshold that recommended by the world health organization for lower and middle income countries.

The strength of this model is the use of relative risk data from a systematic literature review of multiple databases that identified randomized placebo-controlled trials with nine drugs for post-menopausal women [8]. This systematic review includes trials that were identified by a systematic, unbiased literature search.

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Given the lack of head to head trials, the indirect comparison using a Bayesian approach becomes valuable alternative. In addition, the incorporation of quality-of-life issues may be important for clinical decisions from the perspective of Ministry of Health who seek to improve their patients' lives. The present study incorporates a decision analysis approach that compared the cost effectiveness of zoledronic acid versus alendronic acid in women with postmenopausal osteoporosis to assess its cost-effectiveness in order to get reimbursed by the Egyptian Ministry of Health.

The results of the study are supported by many Health Technology Assessment parties. Zoledronic acid was approved by the Scottish Medicines Consortium (February 2008) for use in patients who are unsuitable for or unable to tolerate oral treatment options for osteoporosis [9]. Evidence from Finland, Norway and the Netherlands suggests that zoledronic acid 5mg once yearly infusion was a cost-effective first-line option for osteoporosis in postmenopausal women [10].

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, odds ratio, and fracture costs in the model. To assess the influences of other model structures and assumptions on the cost-effectiveness estimates, one-way sensitivity analyses of various parameters were performed. These various sensitivity analyses did not result in qualitatively different results, and the model proved to be rather robust. The cost-effectiveness of the zoledronic acid versus alendronic acid in this model and its robustness in the sensitivity analysis suggest that the zoledronic acid should be reimbursed by the health care payer (Ministry of Health) in Egypt.

There are some limitations that have to be considered. First; the study doesn't discuss any compliance issues. Compliance is never 100% in oral therapy studies, whereas it should be 100% with infused therapy, in this case, the zoledronic acid due to the fact that it is a single administration for the whole year [4]. One review reported that in a hypothetical choice, the majority of patients preferred annual IV zoledronic acid to frequent oral Bisphosphonates [10,11]. Therefore, Low compliance would be associated with frequent oral Bisphosphonates that can cause 17% increase in the FR and a subsequent 37% increase in the risk of all cause hospitalization which could increase the cost effectiveness of zoledronic acid. Nevertheless, our model did not take into account adherence data during the clinical trials. The persistence during clinical trials was found to be 84% for zoledronic acid [13], 81–89% for alendronic acid [14,15]. Since these values are not reflecting real life setting, we did not include them in our model.

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Second, although Randomized Clinical Trials (RCTs) provide the best available evidence for the relative treatment effect of a particular pairwise comparison, the identified RCTs were only placebo-controlled trials. To obtain insight in the relative efficacy of the new therapy versus a bisphosphonate, we had to rely on indirect comparisons [16]. Third, the time horizon has been limited to 5 years in order to directly use evidence-based clinical data, without any speculation about expected effectiveness over a very long time period, such as a life time horizon. There is no published evidence of longer-term effectiveness data for zoledronic acid necessary to populate such a theoretical model. Once long-term head-to-head clinical evidence becomes available, further modeling approaches will be useful to simulate longer term costs, effectiveness, and cost-effectiveness. It should also be noted that the incorporation of several simplifying assumptions into the model is a weakness, but this weakness was overcome by the sensitivity analyses that encompassed wide ranges of parameter values.

There are other limitations that need to be considered when assessing the relative generalizability of this study. First, we adopted the perspective of the Ministry of Health and not a societal perspective and thus excluded indirect costs and out-of-pocket direct costs incurred by the patient. Accounting for these costs would likely increase the superiority of zoledronic acid because increases in QALYs will lead to reduced absenteeism, increased productivity and recovery, and reduced direct nonmedical costs associated with the follow-up. Second, quality of life values utilized in the model was transferred from the Danish population because we have no outcome data available regarding quality of life values for the Egyptian population. Certain elements of cost-effectiveness studies are transferable. It was based on four steps that consider data availability and methods for adjusting cost-effectiveness information to a particular jurisdiction [17]. Third, ten published articles in English were identified by our electronic search, but we may have omitted some important information that could have been recovered from non-English articles.

The main driver of the cost-effectiveness of zoledronic acid in this model was the increased compliance rate as it is infused over a 15-minute period once a year in zoledronic acid group. This strategy will potentially be applicable to other settings in Egypt because there are no major differences in clinical practices between rural and urban areas; thus, zoledronic acid additional benefit worth the cost that will be reimbursed by the Egyptian Ministry of Health (i.e., good value for money).

- **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 Zoledronic acid is cost-effective alternative to the use of Alendronic acid for management of post-menopausal women with osteoporosis. This means that, compared with alternative, treatment with zoledronic acid gives a

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comparatively high health benefit (improvement in quantity and/or quality of life) for the money spent on treatment.

- **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. Ahmed Hassouna**, Consultant, clinical trials.
- **Prof. Ashraf Nabhan**, Associate Editor, Cochrane Collaboration.
- **Prof. Heba Nassar,** Professor at the Faculty of Economics and Political Science, Cairo University.
- **Dr. Abd Allah Mohammed**, Expert at National Authority for the control of Biopharmaceuticals.
- **Prof. Ayman El-Garf,** Professor of Rheumatology at Faculty of Medicine, Cairo University.
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