Lenalidomide Plus Dexamethasone For Treating Patient With Relapsed Or Refractory Multiple Myeloma

Health Technology Appraisal

Issued: July 2014

- **بيانات المستحضر محل الدراسة:**

Intervention	Lenalidomide + Dexamethasone
Trade name	Revlimid
Company name	Celgene International Sarl
Comparator	Dexamethasone

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضر **Lenalidomide** في علاج مرضي Myeloma المتعددة. 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:**

بخصوص طلب ادارة تسعير الادوية بعمل دراسة "Pharmacoeconomics" لبيان الجدوى الاقتصادية "CEA" لمستحضرRevlimid . وبناءً على رأي اساتذة وخبراء الاورام الذين افادوا بان البروتوكول العلاجي Revlimid + Dexamethasone يمكن مقارنته بعلاج Thalidomide+Dexamethasone في علاج Relapsed Multiple Myeloma.

فقد تبين أن مستحضر Thalidomide لازال تحت التسجيل وغير مسعر جبري وايضا لا يوجد دراسة علمية مقارنة Head to Head Trial حتى يمكن استخدامها في الدراسة الاقتصادية لذا تم استخدام البروتوكول العلاجي Dexamethasone بالمقارنة ب Revlimid + Dexamethasone بناء على الدراسات المنشورة عالمياً:

Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America
Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma

وعليه تبين ان البروتوكول العلاجي Revlimid + Dexamethasone ليس الأكفأ من حيث الفعالية مقابل التكلفة (Not Cost Effective) مقارنة بمستحضر Dexamethasone. ولذا توصي لجنة اقتصاديات الدواء بالتفاوض مع الشركة لعمل 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 "QUALITY OF LIFE" ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالميًا .

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English Summary:

Economic Evaluation Of Lenalidomide Plus Dexamethasone Versus Dexamethasone In Relapsed Or Refractory Multiple Myeloma.

- **Introduction**

Multiple myeloma (MM) is a neoplastic plasma cell disorder that characterized by low blood counts, bone and calcium problems, infections, light chain amyloidosis and other hazards, and its incidence is strongly related to age (1). However, MM isn't curable; it's treatable by chemotherapy combinations that aim to improve survival and quality of life.

Advances in the basic understanding of MM and the development of novel agents, such thalidomide, lenalidomide and bortezomib, have increased therapeutic response rates and prolonged patient survival.

Lenalidomide, immunomodulating agent, belongs to immunomodulatory derivatives class, which are thalidomide derivatives. On the basis of the MM-009 and MM-010 trials, lenalidomide in combination with dexamethasone has been approved by the US Food and Drug Administration and European Medicines Agency for the treatment of MM in patients who have received at least one earlier therapy (2,3,4).

- **Objective**

The objective of the current analysis was to assess the cost-effectiveness of lenalidomide plus dexamethasone versus dexamethasone alone in patients with relapsed or refractory multiple myeloma from the third party payer perspective over a time horizon of ten years.

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- **Economic evaluation Key Features:** [5]

Key Features:	
year of the document	July 2014
Affiliation of authors	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
Purpose of the document	To assess the cost-effectiveness of Len-Dex versus Dex in relapsed or refractory multiple myeloma
Standard reporting format included	yes
Disclosure	yes
Target audience of funding/ author's interests	Public payers, healthcare industries
Perspective	Health care system
Indication	Treatment of relapsed or refractory multiple myeloma
Target population	Both those who are insured and uninsured by the Egyptian health care system.
Subgroup analysis	No Subgroup analysis
Choice of comparator	Dexamethasone
Time horizon	over a ten-year period
Assumptions required	yes
Analytical technique	Cost-effectiveness analysis
Costs to be included	Direct medical costs only; include the cost of therapy, and the cost of AEs treatment, cost of hospitalization, and lab tests for monitoring.
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
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.

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Presenting results	Lenalidomide plus dexamethasone is not clearly cost-effective compared to Dexamethasone; and most likely to result in an ICER higher than the willingness-to-pay threshold.
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**

This cost effectiveness analysis was based on clinical data about complete response rate, time to progression and overall survival derived from a pooled analysis[5] which presents a pooled update of two large, multicenter MM-009 and MM-010 placebo-controlled randomized phase III trials[2,3], that included 704 patients and assessed lenalidomide plus dexamethasone versus dexamethasone plus placebo in patients with relapsed/refractory multiple myeloma (MM).

Results indicated that the addition of lenalidomide to dexamethasone was less likely to be not cost effective when compared with dexamethasone alone based on commonly accepted willingness to pay threshold in Egypt. An incremental cost-effectiveness ratio (ICER) of EGP1,189,452 per QALY gained over time horizon of 10 years.

While the National Institute of Care Excellence (NICE) uses a threshold of £30.000 per QALY[6], we still has no threshold value for cost per QALY gained to conclude whether the new intervention is cost effective against the current intervention or not. WHO proposed many approaches to approximate this threshold. The most common approach is based on 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, whereas one that costs less than once the national annual GDP per capita is considered highly cost–effective.[7] Based on WHO recommendation, the calculated threshold was about EGP70,000[8]. Data on the costs of breast cancer-related health care services, direct nonmedical costs and indirect costs were not collected in these studies.

Like most cost effectiveness evaluations, there are some limitations which need to be discussed. The pooled study we rely on to develop our model based on 2 clinical trials, one of them was an planned interim analysis of safety and efficacy. This preplanned analysis stated that if the predetermined O'Brien–Fleming boundary for the superiority of lenalidomide over placebo was crossed, the study would be unblended and patients would be allowed to cross over and receive lenalidomide at the time of disease progression or at the investigator's discretion.

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In oncology clinical trials, cross over to active treatment upon progression is usually offered to address ethical issues associated with placebo controls. However using efficacy data unadjusted for this cross over may increase decision uncertainty.

According to the Egyptian practice and the national comprehensive cancer network (NCCN) guidelines, thalidomide /dexamethasone is one of the preferred therapies for previously treated multiple myeloma.[10] However, we conducted our analysis against dexamethasone only because of 2 reasons. First, thalidomide still has no market authorization in Egypt. Second, the lack of head to head trial compares lenalidomide plus dexamethasone with thalidomide/dexamethasone. Although using indirect comparison is available in case of absence of head to head comparison, it is associated with uncertainty. This uncertainty may arise from the potential heterogeneity between recruited patients, methods followed in various studies, inclusion and exclusion criteria and possible previous therapy.

The results from the cost-effectiveness analyses conducted by Ruth et. al[11] varied considerably. This study compared lenalidomide/dexamethasone versus dexamethasone alone in managing multiple myeloma (MM) patients who have failed one prior therapy and concluded that LEN/DEX is a cost effective intervention from the perspective of the NHS. The difference in results between the Ruth analysis and our analysis are due to the differences in the current practice and the type of decision analysis selected.

Conclusion

According to the accepted willingness-to-pay threshold in Egypt, using Lenalidomide plus dexamethasone is not clearly cost-effective; and most likely to result in an ICER higher than the societal willingness-to-pay threshold.

- **Declaration of interest**

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

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- **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 in 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. Mohammed Abd Elmoty,** Oncology professor, Faculty of medicine, Cairo University.
- **Dr. Amr Saad, Head of Pharmacovigilance center,** Central Administration for Pharmaceutical Affairs, Ministry of Health.

PEU project team

- **Gihan Hamdy El-sisi**, Head of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.
- **Esraa Saeed,** Team member of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.

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