Palonosetron versus Ondansetron & Granisetron in the Prevention of Chemotherapy-Induced Nausea and Vomiting

Health Technology Appraisal

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- **بيانات المستحضر محل الدراسة:**

Intervention	Palonosetron
Trade name	Aloxi
Company name	Mundi Pharma
Comparator	Ondansetron
Trade name	Zofran
Comparator	Granisetron
Trade name	EM-EX

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضر Aloxi (Palonosetron) في الاستخدام العلاجي chemotherapy-induced nausea and vomiting وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية العالمية وفي ضوء الممارسة الإكلينيكية المحلية. وذلك في ضوء التوصية بإجراء دراسة جدوي اقتصادية COST EFFECTIVENESS بناء علي اجتماع لجنة وحدة إقتصاديات الدواء بالسادة مديري قطاعات الصيدلة بالتأمين الصحي والمؤسسات العلاجية والأمانة العامة للمستشفيات والهيئة التعليمية.

١- خلصت نتائج دراسة الجدوي الإقتصادية عند حساب فارق التكلفة على مدى ٥ أيام بين المستحضرين إلي **أن مستحضر Palonosetron vial (تركيز 0.25mg) عند سعر ٣٤٥.٧١ جنيها هو الأكفأ من حيث الفعالية لقاء التكلفة "cost effectiveness" مقارنة بمستحضر Ondansetron vial (تركيز 8mg) عند سعر ١٥ جنيها.**

وذلك علي الرغم من ان مستحضر Palonosetron هو الأعلي تكلفة بفارق 111.20 جنيه إلا أنه هو الأفضل في تحسين جودة الحياة المعيشية بمقدار QALY 0.087 بالمقارنة بكلا من مستحضر Ondansetron. حيث يتم اعطاء مستحضر Palonosetron جرعة واحدة بينما يؤخذ مستحضر Ondansetron علي أربع جرعات. كذلك فإن معدل الاستجابة الكاملة Complete response في الـ Delayed phase في المرضي المستخدمين لمستحضر palonosetron هو الأعلي من نظيره ondansetron بنحو ٥%.
وبحساب القيمة المتزايدة للتكلفة لقاء الفعالية بلغت 1275.65 L.E/QALY.

٢- **خلصت نتائج دراسة جدوى إقتصادية (cost effectiveness analysis) بين مستحضرى Palonosetron عند سعر ٣٤٥.٧١ جنيه مصري و Granisetron عند سعر٨٤ جنيه مصري الى أن Palonosetron هو الأفضل في تحسين جودة الحياة المعيشية بمقدار ٠.٠٣٦٩٩ QALY .**

وذلك علي الرغم من أن مستحضر Granisetron vial هو الأقل تكلفة حيث أن متوسط تكلفته خلال ٥أيام يُقدر ب ٧٤٧.٢٨ جنيه مصري في حين أن المستحضر Palonosetron يُقدر متوسط تكلفته في نفس المدة ب ٧٧٧.٤٢جنيه مصري على التوالي. وعليه فإن مستحضر Palonosetron vial هو الأفضل من حيث الفاعلية لقاء التكلفة عن مستحضر Granisetron.

وعليه فأن مستحضر Palonosetron vial هو الأفضل من حيث الفاعلية لقاء التكلفة عن المستحضرين الأخريين Ondansetron, Granisetron.

English Summary:

Economic Evaluation Of Palonosetron versus Granisetron in the prevention of chemotherapy-induced nausea and vomiting

- **Introduction**

Chemotherapy-induced nausea and vomiting (CINV) are relatively frequent adverse events during cancer treatments. These symptoms, besides being very debilitating to the patients, have a negative impact on their quality-of-life and are frequently pointed as a major factor for treatment abandonment(1).

The incidence and severity of these effects depend on the inherent emetogenic potential of the chemotherapeutic agents and their dosage and administration schedules, and patient factors such as Younger age, female gender, low use of alcohol, and perceived susceptibility to nausea (2).

The onset of which can be acute (starting within minutes to hours following treatment and generally resolving within 24 h) or delayed (starting more than 24 h after treatment and lasting for up to several days) .Delayed CINV, which tends to be more common than acute CINV, is less responsive to antiemetic therapy. Delayed nausea also tends to be more severe than acute nausea .Although delayed nausea can occur in the absence of acute CINV; both types are important targets for antiemetic therapy because the risk of delayed CINV is greater if acute CINV is poorly controlled. Further, the risk of CINV in general is highly related to its occurrence in a previous cycle of chemotherapy (3).

5-hydroxytryptamine 3 (5-HT3)-receptor antagonists are now the standard therapy for preventing Chemotherapy-induced nausea and vomiting (CINV), because emesis is caused by stimulation of 5-HT3 receptors located on vagal afferents by serotonin released from enterochromaffin cells in the small intestine (4).

The first generation of 5HT3 receptor antagonists (5HT3RAs), such as ondansetron, dolasetron, and granisetron revolutionized CINV management (3). First-generation 5-HT3 RAs are less effective for the treatment of CINV in the delayed phase than in the acute phase. There is therefore an unmet need for more effective therapies to control CINV, which has led to the development of new-generation 5-HT3

RAs such as palonosetron (5).

Palonosetron is a newer 5-HT3 RA with a distinct molecular and pharmacologic profile, including structural differences, stronger binding affinity for the 5-HT3 receptor (2).Palonosetron is a potent, highly selective, second generation 5-HT3 receptor antagonist with an extended plasma elimination half-life (approximately 40 hours), appreciably longer than others in its class (5–9hours) (6). In addition, Palonosetron is able to inhibit 5-HT3/NK1 receptor signaling crosstalk, mediating the prophylaxis of delayed CINV in contradistinction to first-generation 5-HT3 RAs (5).

Objective

To evaluate the cost-effectiveness of Palonosetron compared to Ondansetron and Granisetron in the prevention of Chemotherapy-induced nausea and vomiting from the Health Insurance perspective.

- **Economic evaluation Key Features:[11]**

Key Features:	
year of the document	September 2016
Affiliation of authors	Pharmacoeconomic Unit, Central Administration For Pharmaceutical Affairs
Purpose of the document	Evaluate the Cost-Effectiveness of Palonosetron compared to Ondansetron& Granisetron in the prevention of chemotherapy-induced nausea and vomiting
Standard reporting format included	Yes
Disclosure	Yes
Target audience of funding/ author's interests	Decision makers & the public
Perspective	Health Insurance
Indication	the prevention of chemotherapy-induced nausea and vomiting
Target population	covered patients by the Egyptian health care system
Subgroup analysis	No Subgroup analysis
Choice of comparator	Granisetron &Ondansetron
Time horizon	Over 5days
Assumptions required	Yes
Analytical technique	Cost-utility analysis
Costs to be included	Direct medical costs include costs of treatment and managing strategies according to the Egyptian current practice.
Source of costs	The Ministry of Health 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 QALY
Method to derive utility	Indirect utility from literature using rating scale and standard gamble
Equity issues stated	All lives and life years are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population
Discounting costs	Not done.
Discounting outcomes	Not done.
Sensitivity analysis-parameters and range	Critical component(s) in the calculation is varied
Sensitivity analysis-methods	One-way sensitivity analysis is performed.
Presenting results	Palonosetron is cost-effective intervention compared to granisetron and ondansetron in the prevention of chemotherapy-induced nausea and vomiting
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.

- **Discussion**

It is important to identify the most cost-effective prevention of cancer induced nausea and vomiting. To support reimbursement decision-making in Egypt, decision analysis, a quantitative method for synthesizing data from numerous sources for the evaluation of treatment alternatives was developed to determine the cost-effectiveness of the palonosetron compared to ondansetron and granisetron.

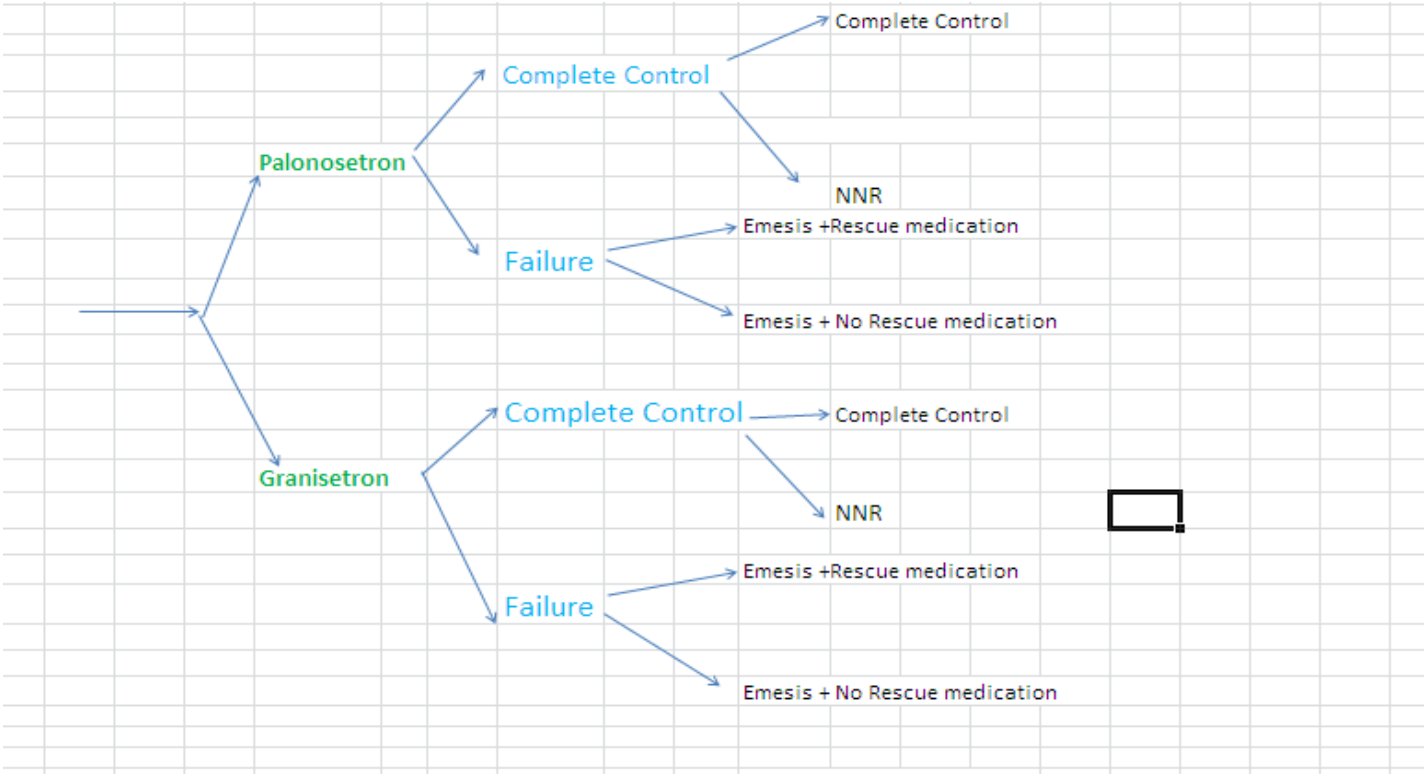
The literature search was conducted in Medline, PubMed and Cochrane Library to identify relevant published English articles from 2005 to 2016. The decision analytical model was constructed to assess the costs and consequences associated with palonosetron compared to ondansetron and granisetron.

The pooled data from literature indicate palonosetron (0.25 mg or 0.75mg) is more effective in preventing nausea than ondansetron, dolasetron, or granisetron. It is likely the pharmacokinetic and pharmacodynamics properties of palonosetron contribute to the apparent improvement over older 5-HT3 RAs in preventing nausea in the delayed post chemotherapy phase (2). The most noteworthy differences between palonosetron and older 5HT3 RAs occurred in the delayed phase and throughout the overall 5-day evaluation period. Palonosetron therefore provides an effective option for delayed onset CINV, an effect of chemotherapy that previously had been more difficult to manage due to the limited efficacy of older 5HT3 RAs in this context. Further, palonosetron may be more effective in controlling nausea (particularly delayed nausea), which remains a

challenge despite the antiemetic efficacy of the older 5HT3 RAs. The observed advantage of palonosetron in efficacy during the delayed phase may be explained by differences in binding characteristics of palonosetron (i.e., a longer elimination half-life relative to other 5HT3 RAs and triggering of receptor internalization leading to prolonged inhibition of receptor function and NK1cross talk). All of the studies evaluated outcomes following a single dose of palonosetron or other 5HT3 RAs given on day 1 of chemotherapy; outcomes may differ with the use of multi-day antiemetic treatment regimens (3).

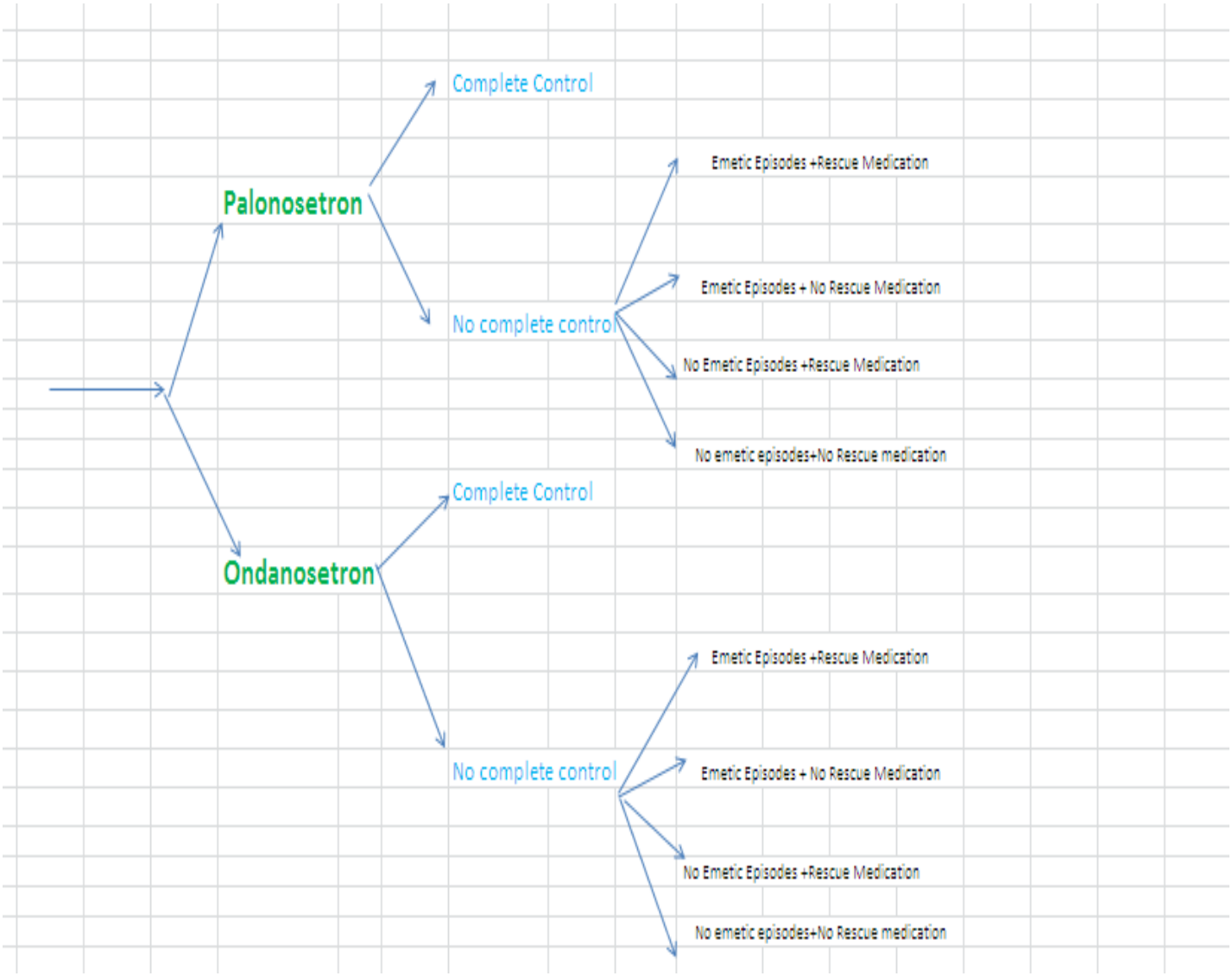
The clinical parameters of the model of palonosetron versus granisetron were derived mainly from phase III, multicenter, randomized, double-blind, double-dummy, stratified, parallel-group, active-comparator trial from 75 institutions in Japan. There was 1114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. Patients were followed up, for 5 days. Primary endpoints were the proportion of patients with a complete response (defined as no emetic episodes and no rescue medication) during the acute and the proportion of patients with a complete response during the delayed phase (24–120 h post chemotherapy; superiority comparison with granisetron) (4, 5).

Figure 1 : illustrating the decision tree model for the cost effectiveness study of palonosetron versus granisetron.



The clinical parameters of the model of palonosetron versus ondansetron were derived mainly from trial based economic evaluation performed on 374 patients, comparing palonosetron to ondansetron. Patients were followed up, for 5 days. the primary endpoint was the complete response (CR) rate defined as the proportion of patients with no emetic episodes (EEs) and no need for Rescue Medication (RM) during 24 hours following chemotherapy administration (acute phase). Secondary endpoints included efficacy in the prevention of delayed (days 2–5 post-chemotherapy) and overall (days 1–5 post-chemotherapy) CINV, number of EEs and time to RM treatment (7).

Figure 2 : illustrating the decision tree model for the cost effectiveness study of palonosetron versus ondansetron. .



The utility values of the model of palonosetron versus granisetron, event duration and decrement from perfect health used in the model were obtained from a published prospective study to determine utility scores for control of chemotherapy-induced nausea or vomiting from 70 women with ovarian cancer using a modified visual analog scale (8).

The utility values of the model of palonosetron versus ondansetron, event duration and decrement from perfect health used in the model were obtained from a published multicenter prospective study to determine utility scores for control of chemotherapy-induced nausea or vomiting from 96 subjects using rating scale technique. The rating scale (feeling thermometer) is perhaps the most straightforward technique, since this technique merely requires a linear ranking of the health states in question. The rating scale was able to establish a rank order among the various degrees of nausea and vomiting. However, the standard gamble revealed little difference in utility among health states of limited morbidity, for reasons that may be intrinsic to this technique (9).

Direct medical costs were obtained from the Ministry of Health hospitals in Egypt. Deterministic Sensitivity analyses were conducted. Total costs for Palonosetron and Granisetron were EGP 777.417551 and EGP 747.2827413 respectively. QALYs for Palonosetron and Ondansetron were 1.24346 and 1.20647 respectively. The incremental cost-effectiveness ratio (ICER) for Palonosetron versus granisetron was L.E 814.57227 EGP/QALY. This study showed that Palonosetron is a cost effective choice compared to Granisetron in the prevention of chemotherapy-induced nausea and vomiting. One way sensitivity analysis showed that percentage of patients failed complete response of delayed phase for granisetron has the greatest impact on the results.

Total costs for Palonosetron and Ondansetron were EGP 354.199 and EGP 94.991 respectively. QALYs for Palonosetron and Ondansetron were 1.577833505 and 1.490655907 respectively. The incremental cost-effectiveness ratio (ICER) for Palonosetron versus Ondansetron was L.E 2973.330 EGP/QALY. This study showed that Palonosetron is a cost effective choice compared to Ondansetron in the prevention of chemotherapy-induced nausea and vomiting. One way sensitivity analysis showed that percentage of patients with complete response, no nausea and no vomiting, of delayed phase for ondansetron has the greatest impact on the results.

Several limitations of the present study deserve to be mentioned. The dosage of ondansetron used in the clinical trial (a single 32mg IV dose) is currently not the most common treatment regimen, but in costing terms it is broadly comparable to or cheaper than the regimens which typically are used, such as ondansetron 8mg initially and then 8mg every 6 hours for 120 hours.

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 plausible ranges of the probability of rescue medication, and drug costs based on published sources. To assess the influences of other model structures and assumptions on the cost-effectiveness estimates, one-way sensitivity analyses of various parameters were performed. The Deterministic sensitivity analysis demonstrated that

percentage of patients with complete response, no nausea and no vomiting, of delayed phase for ondansetron has the greatest impact on the results & percentage of patients failed complete response of delayed phase for granisetron have the greatest effect on the results. These various sensitivity analyses did not result in qualitatively different results, and the model proved to be rather robust.

- **Conclusion**

Results from this study suggest that employing a Palonosetron is a cost-effective intervention compared to Granisetron and Ondansetron in the prevention of chemotherapy-induced nausea and vomiting, , based on the willingness to pay threshold stated by world health organization (3xGDP/capita) for low and middle income countries. These findings will help inform health care decisions regarding the allocation of health care system resources to improve the health of the Egyptian population.

- **Declaration of interest**

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

- **PEU project team**

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

- **Zeinab Ahmed El shafei,** Team member of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.

- **Asmaa saad,** Team member of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.

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