Sapropterin Dihydrochloride For Patients With Phenylketonuria In Egypt

Health Technology Appraisal

Issued: October 2013

- **بيانات المستحضر محل الدراسة:**

Intervention	Sapropterin Dihydrochloride
Trade name	Kuvan
Company name	Merck Serono
Comparator	Phenylalanine Free Diet

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضر **Sapropterin Dihydrochloride** في علاج مرضي الفينيل كيتونيوريا. 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:**

تقترح اللجنة دراسة الـ Risk Sharing Agreement الخاصة بمستحضر الـ Kuvan، وذلك في ضوء ما أسفرت عنه الدراسة الاقتصادية الاسترشادية التي قامت بإجرائها وحدة اقتصاديات الدواء لتحليل القيمة مقابل التكلفة لمستحضر Kuvan مقارنة Phenylalanine (PHE) free diet.

حيث أظهرت النتائج أن السعر المناسب لمستحضر Kuvan الذي يحقق أعلى قيمة علاجية مقابل التكلفة المدفوعة هي ٢,٧٧٢ جنيه مصري، كما أسفرت الدراسة أيضًا أن مستحضر Kuvan لا يحقق القيمة العلاجية مقابل التكلفة في مرضى Phenyl Ketonurea اذا تم الاتفاق على السعر المقدم من الشركة للتأمين الصحى.

- علما ان الدراسة التي قامت باجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالالبان التى تحتوى على PHE free diet التي تم تجميعها من وزارة الصحة اما التكلفة الخاصة بالدواء تم أحتسابها بناء على السعر الجبرى للمستحضر، كما تم تجميع البيانات الخاصة بالقيمة العلاجية لكلا النوعين من الدراسات المنشورة عالميًا.

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English Summary:

Cost-Effectiveness of Sapropterin versus Phenylalanine Free Diet in Patients with Phenylketonuria in Egypt

- **Introduction**

Phenylketonuria (PKU) is an inherited metabolic disease characterized by phenylalanine (Phe) accumulation, in which the enzyme phenylalanine hydroxylase (PAH) does not function properly, which helps the body to break down Phe. This genetic disease can lead to neurocognitive and neuromotor impairment as mental retardation, behavioral abnormalities, seizures, an inability to focus and organize information, and other neurologic complications.

PKU is an orphan disease with incidence rate 1:5000 in Egypt. Sapropterin dihydrochloride, an FDA-approved synthetic formulation of tetrahydrobiopterin (6R-BH4, herein referred to as sapropterin) is effective in reducing plasma Phe concentrations in patients with hyperphenylalaninemia due to tetrahydrobiopterin (BH4)-responsive PKU, offering potential for improved metabolic control [1].

- **Objective**

Phenylketonuria (PKU) is an orphan disease with incidence rate 1:5000 in Egypt. Cost-effectiveness of Sapropterin versus Phenylalanine (PHE) free diet in PKU patients from the insurer perspective was evaluated over a time horizon of 10 years.

- **Economic evaluation Key Features:[2]**

Key Features:	
year of the document	October 2013
Affiliation of authors	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
Purpose of the document	Evaluation the cost-effectiveness of using Sapropterin compared to Phenylalanine (PHE) free diet in PKU patients
Standard reporting format included	yes
Disclosure	yes
Target audience of funding/ author's interests	Public, healthcare industries and clinicians
Perspective	Insurer perspective
Indication	Treatment of Phenylketonuria

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Target population	Those who are 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	Phenylalanine (PHE) free diet
Time horizon	over a ten-year period
Assumptions required	yes
Analytical technique	Cost-utility analysis
Costs to be included	Total costs include costs of treatment and managing complications 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
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	Sapropterin doesn't represent a good value for money compared to PHE free diet in the Egyptian PKU patients
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.

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- **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 Sapropterin as compared to, the currently used regimen, Phenylalanine Free Diet.

Initiating Sapropterin is likely to improve the management of patients with PKU. Our results demonstrate that Sapropterin versus Phe free diet is not cost effective for patients with mild and classical PKU. Interestingly, Sapropterin group showed small incremental effects when compared with Phe free diet. At the same time, costs associated with Sapropterin group are higher than costs associated with Phe free diet group.

The strength of our model is the use of relative risk data from a 22-week, multicenter, open-label randomized placebo-controlled study on eighty patients [1]. In addition, incorporating quality of life issues may be important in clinical decisions. The epidemiologic parameters part of our analysis was supported by publications conducted in Egypt [2,3]. As well as the decision analysis approach on Sapropterin are lacking, this study is the first to incorporate a decision analysis approach comparing the cost-effectiveness of Sapropterin versus Phe free diet in patients with PKU.

In our analysis, we explicitly took model inputs uncertainty into account by assigning plausible ranges to quality of life, relative risk and epidemiologic parameters in the model. This allowed us to perform one way sensitivity analysis that showed no impact on the results. To assess the influence of other model structures and assumptions on the cost-effectiveness estimate we performed one-way sensitivity analyses on various parameters. Various sensitivity analyses did not result in qualitative changes of our results, and the model proved to be rather robust. In a situation where a decision has to be taken, the only rational way for a risk-neutral decision-maker is not to adopt Sapropterin strategy unless there is a cut in Sapropterin price.

There are some limitations that need to be considered when assessing its relative generalizability. First, the additional costs of sapropterin are difficult to estimate due to variations in weights of children so the perspective was that of an insurer perspective and not a societal one and as such we excluded indirect costs or out-of-pocket direct costs incurred by the parent of the patient. Second, our analysis was mainly based on effectiveness data from one RCT comparing Sapropterin versus Phe free diet in patients with PKU.

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On the basis of the available evidence, our results are likely to be similar to the National Centre for Pharmacoeconomics (NCPE) in Ireland who didn't recommend sapropterin as an add-on treatment for patients with PKU as well as the Pharmaceutical Benefits Advisory Committee (PBAS) in Australia and National health service (NHS) in Britain rejected the submission for sapropterin because of uncertainty around the clinical place in therapy and high and uncertain cost effectiveness. Current dietary management with a phenylalanine-free diet remains the intervention of choice [4,5,6]. The main driver of the absence of a demonstration of Sapropterin cost-effectiveness from this model is that the Cost per QALY data is unavailable due to the paucity of quality of life data in the literature and the high price of Sapropterin Tablets.

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, and 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.

- **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. World Health Organization recommends that interventions that cost more than 3 times GDP/capita for one Disability Adjusted Life Year (DALY) avoided should not be reimbursed. Despite the difference between DALY and QALY, one can assume they are similar to be able to put a value on the outcome.

This means that, compared with alternative uses of scarce health care resources, Sapropterin doesn't represent a good value for money compared to PHE free diet in the Egyptian PKU patients. Whether Sapropterin is cost-effective in certain subgroups needs to be addressed in future studies.

- **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 for this appraisal appears below:

- **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. Rasha Hassan**, director of pricing administration Central Administration for Pharmaceutical Affairs, Ministry of Health.
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- **PEU project team**

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

- **References:**

1-Lee P, Treacy EP, Crombez E, et al. Safety and Efficacy of 22 Weeks of Treatment with Sapropterin Dihydrochloride in Patients with Phenylketonuria. American Journal of Medical Genetics 2008; 146:2851–2859.

2- Elsisi GH, Kaló Z, Eldessouki R**,** Elmahdawy MD, Saad A, Ragab S, Elshalakani AM, Abaza S. Recommendations for Reporting Pharmacoeconomic Evaluations in Egypt. Value in Health for Regional Issues 2013.

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3-El Araby H, Fateen E, Gouda A. Screening for phenylketonuria and galactosemia among Egyptian newborns in Menoufiya governorate. Egypt. J. Med. Hum. Genet. 2009;10:2.

4-National Centre for Pharmacoeconomics. Sapropterin (Kuvan) for the treatment of phenylketonuria (PKU); June 2009.

5-East Midlands Specialised Commissioning Group Website. http://www.emscg.nhs.uk/Library/EIASapropterin.pdf

6-Australian Government, Department Of Health And Ageing website.
http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-outcomes-and-public-summary-documents

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