Sorafenib in the Treatment of Advanced Hepatocellular Carcinoma

Health Technology Appraisal

Issued: January 2017

- **بيانات المستحضر محل الدراسة:**

Intervention	Sorafenib
Trade name	Nexavar
Company name	Bayer Schering
Comparator	Best Supportive Care

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضرSorafenib في علاج مرضي سرطان الكبد المتقدم. وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية العالمية وفي ضوء الممارسة الإكلينيكية المحلية.

- علما ان الدراسة التي قامت باجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضرات والتي تم تجميعها من مناقصات هيئة التأمين الصحي، بالاضافة إلى باقي التكلفة المرتبطة بالإقامة بالمستشفى والأدوية والتبعات المحتملة عن علاج حالات سرطان الكبد المتقدم والناتجة عن استخدام كل بروتوكول على حدة، وطبقا لتسعيرة نفقة الدولة.

كما تم تجميع البيانات الخاصة بنسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالميًا

بعد البحث في الأدلة العلمية وبناء علي دراسة الجدوي الإقتصادية التي أجريت من قبل الوحدة وبالعرض علي وحدة إقتصاديات الدواء تبين ان مستحضر Sorafenib هوالأكثر في التكلفة مقارنة بـBSC في علاج مرضي سرطان الكبد المتقدم حيث ان مستحضر Sorafenib هو الاعلى فى التكلفة بفارق 9,906,475 جنيه مصري واكثر فى الفاعليه بفارق 0.869655963 مقارنة ب BSC .

English Summary:

Cost-Effectiveness of Sorafenib versus BSC in the treatment of Advanced Hepatocellular Carcinoma in Egyptian Patients from the Insurer perspective: A Markov Model

- **Introduction**

Hepatocellular carcinoma (HCC) is the most common form of liver cancer and is a major health problem accounting for more than 626 000 new cases per year worldwide (1, 2). Most of HCC burden lies in developing countries. The regions of high incidence include Eastern and South-Eastern Asia, Middle and Western Africa. Worldwide, it is the third most common cause of cancer death with mortality to incidence ratio of 0.93 (3). In Egypt, liver cancer ranks fourth among all cancers representing 8% of total cancers in both sexes. It is the second cause of cancer mortality representing 10.5% of cancer deaths (3).

Risk factors for HCC are numerous and include hepatitis B and C infections (HBV and HCV), cirrhosis, aflatoxins, alcohol, smoking and male gender (4). These risk factors vary among countries, but chronic infections with HBV and HCV are the most important precursors for HCC development on a global scale. Together, HBV and HCV infections account for over 80% of HCC cases worldwide (5). In Egypt, HCV is the main risk factor for HCC where 71% of HCC cases are positive for anti-HCV antibodies (6).

Despite the increase in overall incidence, treatments for HCC are limited. Potentially curative therapies such as resection, liver transplantation and percutaneous ablation are only available for early stages of disease and, even then, are only applicable for 30–40% of cases(7).

In patients with HCC who progress after locoregional therapy or are diagnosed at advanced stages, there is no standard treatment. Given the lack of effective treatment, HCC is a clinical area associated with high unmet need.

Sorafenib a multikinase inhibitor is the first and only systemic therapeutic agent to receive approval by the FDA for the treatment of unresectable HCC (8).Therefore, BSC was used as the comparator in the economic model. This assumption was confirmed with Egyptian oncologists, and is also consistent with the conclusions of the European Association for the Study of the Liver (EASL) panel of experts for HCC (9), which have further been endorsed by the American Association for the Study of Liver Diseases (AASLD) (10).

In evaluating comparable treatments, it has become increasingly important to understand not only efficacy but the costs of interventions aimed at reducing mortality and morbidity of critically ill patients. The study was conducted to evaluate the cost-effectiveness of Sorafenib to help guidance in the decision-making of the reimbursement process of these drugs.

- **Objective**

The objective of this study was to evaluate the cost-effectiveness of Sorafenib versus BSC in the treatment of Advanced Hepatocellular Carcinoma from the health care system perspective over a time horizon of 4 years.

- **Economic evaluation Key Features:**

Key Features:	
Title and year of the document	December 2016
Affiliation of authors	Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs
Purpose of the document	Evaluation the cost-effectiveness of using Sorafenib versus BSC in the treatment of Advanced Hepatocellular Carcinoma in Egyptian patients
Standard reporting format included	yes
Disclosure	yes
Target audience of funding/ author's interests	Public health care system
Perspective	Health care system
Indication	treatment of Advanced Hepatocellular Carcinoma
Target population	Insured patients by the Egyptian health care system
Subgroup analysis	No sub group analysis
Choice of comparator	BSC
Time horizon	4 years
Assumptions required	yes
Preferred 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	The Health insurance & MoH Hospitals
Modeling	Markov model
Systematic review of evidences	yes
Preference for effectiveness over efficacy	yes
Outcome measure	Life years gained
Method to derive utility	-
Equity issues stated	All lives, life years, are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population

Discounting costs	yes
Discounting 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	Sorafenib is more costly and more effective compared to BSC for management of Advanced Hepatocellular Carcinoma
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**

Sorafenib is the first agent to demonstrate a statistically significant increase in overall survival as compared to BSC in patients with HCC. The aim of this analysis was to assess the cost-effectiveness of sorafenib against BSC in patients with Advanced Hepatocellular Carcinoma from the perspective of the Health care system.

A Markov model was constructed to assess the costs and consequences associated with Sorafenib compared with BSC in the treatment of HCC. After conducting literature search in Medline, PubMed and Cochrane Library to identify relevant published English articles from January 2000 to October 2016, the clinical parameters were derived mainly from a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial that compares Sorafenib versus BSC on 602 patients from 121 centers in 21 countries with Advanced HCC (11).

The model structure is consistent with clinical practice and, together with the assumptions, and was validated by clinical experts. It is also in line with other economic models developed in oncology, with the main health states of alive without cancer/progression, alive with cancer/progression and dead. The model used monthly cycles to match treatment patterns and the continuous nature of the administration of Sorafenib, i.e. patients have the possibility to change from one health state to another every month.

Patients received first-line treatment (sorafenib or BSC) until documentation of disease progression or until a treatment-limiting adverse event (AE) occurred. At the point of progression, patients on sorafenib could either continue on first-line treatment with sorafenib or switch to BSC (palliative care). Patients on first line treatment with BSC continued on BSC post progression. At any point in the model, patients could die due to all-cause (general) mortality.

Health effects are expressed in terms of life-years (LYs) gained. The analysis calculates incremental cost–effectiveness ratios (ICERs) as cost per LY gained. The health effects are based on the outcomes measured in the SHARP trial (11). Dosage of Sorafenib was based on the Phase III trial for those drugs. The daily recommended Sorafenib dose was 400 mg (consisting of two 200-mg tablets) twice daily.

The resource use estimates and unit costs in Egyptian pounds (direct medical costs) were obtained from the health insurance hospitals in Egypt and were used to calculate the total cost of managing HCC patients for each health state in the model and the treatment of grade 3 or 4 AEs. All costs and outcomes occurring beyond 1 year were discounted at 3.5%.

Total costs for Sorafenib and BSC were EGP 10,497,937and EGP 591,461 respectively. LYG for Sorafenib and BSC were 0.879 and 0.0099 respectively. The incremental cost-effectiveness ratio (ICER) for Sorafenib versus BSC was L.E 11,391,257 /LYG. This study showed that Sorafenib is more effective and more costly compared to BSC in treating Advanced Hepatocellular Carcinoma.

The main strengths of this study are the use of evidence from prospective, multicenter, parallel randomized study. Data constraints lead to certain limitations within the model. First, with most economic models, the analysis is based on multiple data sources and reliant on the application of analytical assumptions. A second limitation of the study concerns the absence of quality of life estimation in the model. This is due to the highly variable range of utility values available in the literature which do not match the health states in the model or trial population.

The results of this model wasn't comparable with another cost effectiveness studies performed in Canada and US which showed that Sorafenib for treatment of Advanced Hepatocellular Carcinoma.was cost effective over a lifetime horizon, ratios within the established threshold that society is willing to pay.

In order to identify model drivers and examine key areas of uncertainty within the model, one-way sensitivity analyses were provided for all major model variables. In this analysis, we explicitly accounted for these uncertainties by assigning confidence intervals and plausible ranges based on published sources. The analyses showed that Sorafenib median time to radiological progression, Sorafenib median post progression survival and monthly cost of Sorafenib had the greatest impact on the results.

- **Conclusion**

  Results from this study showed that Sorafenib is more effective and more costly compared to BSC in treatment of Advanced Hepatocellular Carcinoma in Egyptian patients. These findings will help inform health care decisions regarding the allocation of health care system resources to introduce better outcomes for 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.

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