Deferasirox for the Treatment of High Levels of Iron in the Blood in B-Thalassemia Patients

Health Technology Appraisal

Issued: September 2016

- **بيانات المستحضر محل الدراسة:**

Intervention	Deferasirox
Trade name	Exjade
Company name	Novartis
Comparator	Deferiprone (Ferriprox Syrup)

- **الهدف:**

تقييم الفعالية لقاء التكلفة لمستحضر Deferasirox (Exjade) في الاستخدام العلاجي Iron chelation therapy في مرضي B-Thalassemia، 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.

- **توصية لجنة اقتصاديات الدواء:**

في ضوء متابعة إجراء دراسة الجدوي الإقتصادية لتحديد القيمة العلاجية المضافة مقابل التكلفة لمستحضر Deferasirox مقارنة بمستحضر Deferiprone شراب في المرضي الأطفال وفقا لتعديل السؤال البحثي المقدم من اساتذة أمراض الدم بالتأمين الصحي واستنادا للبرتوكول العلاجي المطبق بالتأمين الصحي.

- خلصت نتائج دراسة التكلفة المتزايدة لقاء الفعالية علي مدار ٢٠ عاما إلى أن مستحضر Deferasirox (Exjade) عند عرض السعر المقترح من الشركة وهو ١٠٣٣ جنيه للعلبة (٢٨ قرصا تركيز 500 mg) هو الأكفأ من حيث الفعالية لقاء التكلفة "cost effective" في علاج تراكم الحديد بالجسم في مرضي Beta Thalassemia مقارنة بمستحضر Deferiprone (Ferriprox syrup) عند سعر ٥٥٠ للعلبة الشراب تركيز 100mg .

وذلك علي الرغم من ان Deferasirox هو الأعلي تكلفة إلا أن له الأفضلية في تحسين جودة الحياة المعيشية للمرضي مقارنة بمستحضر Deferiprone وذلك لارتفاع نسبة الـ non compliance بين المرضي الأطفال في Deferiprone شراب إلي ٧.٨%، وتعاطيه ثلاثة جرعات يوميا بدلا من إعطاءه قرصا واحدا يوميا كما في مستحضر Deferasirox .

- **علما ان الدراسة التي قامت بإجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضرات والتي تم تجميعها من التأمين الصحي، بالإضافة إلى باقي التكلفة المرتبطة بالأدوية والفحوصات الدورية وباقي التبعات المحتملة عن استخدام كل بروتوكول علاجي على حدة.**
- **تم تجميع البيانات الخاصة بالقيمة العلاجية الناتجة عن جودة الحياة المعيشية للمريض utility ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالميًا .**

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

English Summary:

Economic Evaluation Of Deferasirox Versus Deferiprone For The Treatment of High Levels of Iron in The Blood In Egyptian Thalassemia Patients

- **Introduction**

Beta thalassemia is a blood disorder that reduces the production of hemoglobin. Hemoglobin is the iron-containing protein in red blood cells that carries oxygen to cells throughout the body. It has been estimated that over 42,000 newborns are affected by Beta-thalassemia every year worldwide. In Egypt, B-thalassemia creates a financial burden on the patients' family and the society (1).

Although regular blood transfusions can prevent death and decrease mortality, patients are at risk for excessive iron accumulated from transfused red blood cells which can lead to organ failure (2). In the absence of chelating therapy, the accumulation of iron results in progressive dysfunction of the heart, liver, and endocrine glands (3).

Choice of an appropriate iron chelator for transfusion-dependent patients, is an important step to reduce iron overload, allow normal growth, prolong life and may improve the overall prognosis. Deferoxamine (DFO) was considered as "gold standard" for the last three decades, clinical experience demonstrated that parenteral DFO treatment was insufficient to reduce cardiac iron burden and had low compliance in patients (4). Oral iron chelators, such as Deferiprone (DFP) and Deferasirox (DFX), are potentially improve cardiac and endocrine function, reduces liver iron and serum ferritin concentration, reduce cardiac mortality, and improve survival (5, 6).

Strategies of oral chelation using are needed to monitor the effectiveness of chelation therapy and their side effects. Although DFP has good compliance, some serious side effects such as gastrointestinal disturbances, Arthropathy, Neutropenia and Agranulocytosis were reported. While DFX have the advantage of taking a once-daily and typically well tolerated, with adverse events generally being mild (7, 8, 9, 10).

Objective

To evaluate the cost-effectiveness of Deferasirox (DFX) compared to Deferiprone (DFP) in B-Thalassemia patients with high levels of iron in the blood from the Health Insurance perspective.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

- **Economic evaluation Key Features:[12]**

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 using DFX versus DFP for the treatment of iron overload
Standard reporting format included	Yes
Disclosure	Yes
Target audience of funding/ author's interests	Ministry of Health perspective
Perspective	Health Insurance
Indication	Treatment of iron overload in the blood
Target population	Insured patients by the Egyptian health care system
Subgroup analysis	No Subgroup analysis
Choice of comparator	DFP
Time horizon	Over 20-year period
Assumptions required	Yes
Analytical technique	Cost-effectiveness analysis
Costs to be included	Direct medical costs include costs of treatment and managing strategies according to the Egyptian current practice.
Source of costs	Health Insurance and Ministry of Health Hospitals
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 QALY
Method to derive utility	Using the published literature (time-trade-off method)
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	A discount rate of 3.5 % per year
Discounting outcomes	A discount rate of 3.5 % per year
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	DFX strategy is cost-effective intervention compared to DFP in patients with iron overload
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**

Cost-effectiveness analysis is useful in countering the financial uncertainties and treatment efficacy concerns faced by decision makers in the health sector and in selecting the most appropriate therapy for given patients. Ideally, comparative effectiveness research will serve its purpose in combating rising health-care costs, resulting in significant savings and positive health outcomes for patients

- Study Design

A Markov model with three health states (Fig.1) was used to estimate the incremental cost effectiveness of DFX compared with DFP. B-thalassemia Patients began in states based on the developing of cardiac complication. In those patients, cardiac complications represent the primary cause of mortality and one of the major causes of morbidity [11]. They could stay at the same health state "alive without cardiac complication", transition to another health state "alive with cardiac complication", or die of natural causes.

Analysis was conducted from Health Insurance perspective. A time horizon of 20 years, with a cycle length one year, was used in order to capture long-term complications and their associated costs. All costs and benefits were discounted by 3.5 %, following the recommendations of the Egyptian guidelines for reporting pharmacoeconomic evaluations [12].

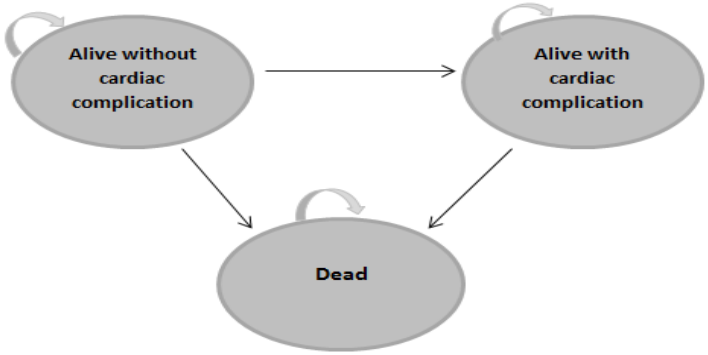

Figure 1: Markov model

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

- **Clinical and cost data**

The literature search was conducted in Medline, PubMed and Cochrane Library to identify relevant published English articles from January 2003 to September 2016. The clinical parameters were derived mainly from the published literature two retrospective trials. The first trial was performed on 550 Thalassemic patients, who are on Deferasirox, Deferiprone and Deferoxamine. Patients were followed up for 6 years. The finding has been confirmed that the Combination therapy (Deferoxamine and Deferiprone) is best in reducing both cardiac and hepatic iron, while mono-therapy with Deferiprone or Deferasirox are effective in the heart and liver respectively [9].

While in the second trial, patients were followed up, on average, for 6 years. At the end of the study, cardiac dysfunction, expressed as worsening of pre-existing cardiac abnormality or development of new cardiac disease, was diagnosed in 2 (4%) of the 54 Deferiprone-treated patients and in 15 (20%) of the 75 Deferoxamine-treated patients, from the first to the last measurement p = 0.007 [13].

The utility values, event duration and decrement from perfect health used in the model were obtained from both the published literature and the expert opinion about local practice. The effect of the administration of iron chelation therapy on quality of life has been examined by a study in the United Kingdom, using a time-trade-off method [14]. The respondent sample was recruited from an International database of 73,000 subjects, to be representative of the UK population, based on gender, age, education and income.

This study estimated a utility score of 0.66 for SC DFO and 0.84 for oral DFX. No data were identified regarding the utility of Deferiprone therapy. Assumptions regarding the utility conferred by Deferiprone are required; in view of the high degree of uncertainty, mean of utility values (ranging from 0.66 to 0.84) is adapted based on the most relevant systematic review and economic evaluation available [15].

Of the nine published economic analyses, only one study included adverse events. Only AEs specifically mentioned as areas of concern within the summaries of product characteristics were included in this model [16]. DFP is associated with agranulocytosis and neutropenia events, with the SPC quoting rates of 0.6 and 2.5 per 100 patient-years, respectively. These were converted into annual rates of 0.6 and 2.5 %. While DFX is associated with a hepatitis rate of 0.7 % assumed based on the DFX prescribing information.

The decision to exclude adverse events was primarily due to the fact that the rate of adverse events is very low due to monthly monitoring of complete blood profile or neutrophil count and both kidney and liver function. Also, considering discussions with clinicians about the current clinical practice in Egypt indicate that in majority of cases, adverse events associated are mild and self-limiting and these abnormalities almost always resolve following drug discontinuation for a transit period. These local applied policies with regards to treating patients suffering from an adverse event are incorporated into our economic evaluation.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

Direct medical costs were obtained from the Health Insurance and Ministry of health hospitals in Egypt. As this model is chosen to take Health Insurance perspective and therefore only included the costs borne by the health-care system. These costs include the costs of chelation therapy, monitoring tests and administration if found. Deterministic sensitivity analyses and discounting were conducted.

Table 1: Model Inputs Paramters

Inputs parameters	Input Value	Reference
Annual Probabilities		
Mortality w/cardiac complication	0.163339973	16
Natural mortality	0.00039	17
Developing cardiac disease	0.010153599	12, 16
Annual utility		
utility-Deferasirox (DEX)	0.84	13, 14
utility-Deferiprone (DFP)	0.75	13, 14
Annual treatment and monitoring cost		
DEX (500mg/28tab) cost	13465	company file
DFP syrup(500mg/100ml) cost	6022	company file
Serum ferritin test /q3mo	120	health insurance hospitals
Complete blood profile	450	health insurance hospitals
ECHO	60	health insurance hospitals
Serum creatinine test	120	health insurance hospitals
Liver function test	360	health insurance hospitals
Percentage of noncompliant patient on DFO	7.8%	18
Discount rate of costs & outcomes	3.5%	11

- **Results**

Total costs for DEX and DFP were EGP 18,549,995 and EGP 9,258,051 respectively. QALYs for DEX and DFP were 1160.542 and 1002.590 respectively. The incremental cost-effectiveness ratio (ICER) for DEX versus DFP was L.E 58,827 EGP/QALY. This study showed that DEX is a cost effective choice compared to DFP in the removing iron overload in Thalassemia Patients.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
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- **Sensitivity Analysis**

The effect of parameter uncertainty was explored in sensitivity analysis. The parameters [in Table 1] were varied over the ranges specified in one-way sensitivity analysis. It showed that the utility of patients with of drugs has the greatest impact on the results [figure 2].

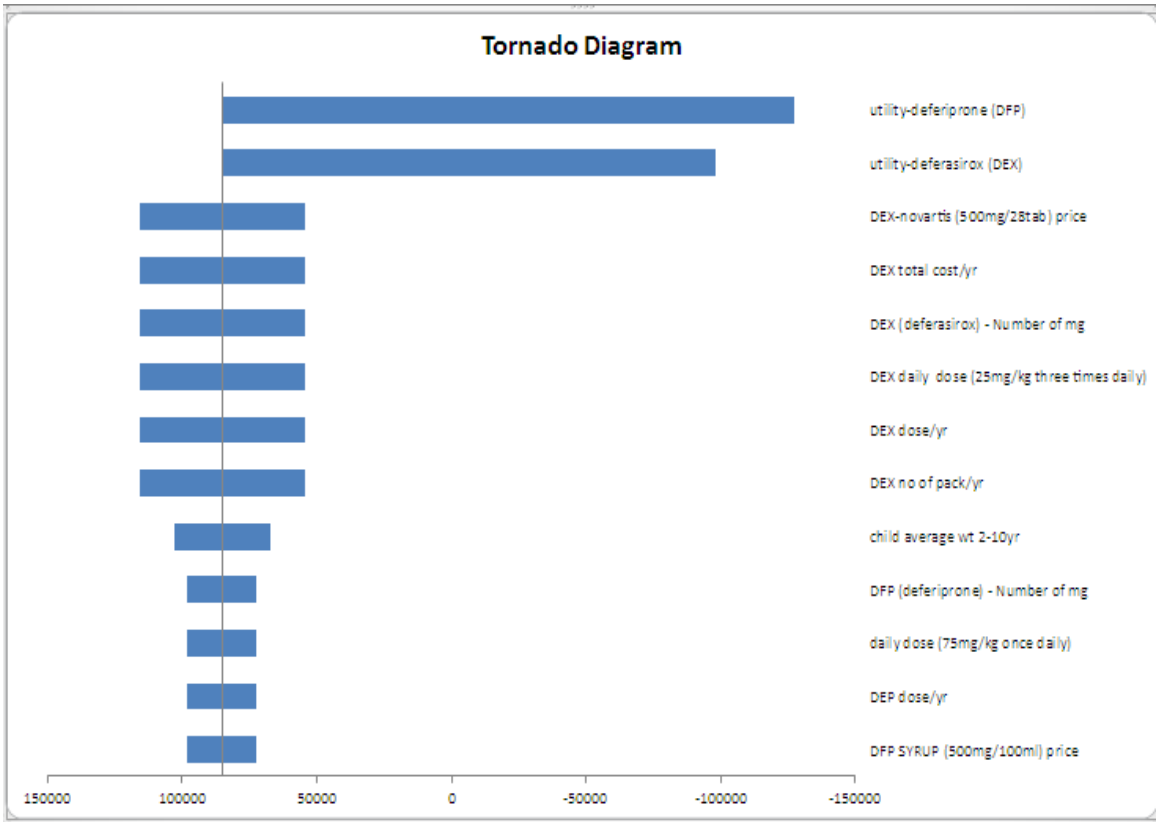

Figure 2: one way sensitivity analysis chart

- **Discussion**

Although one strength of our analysis is the robustness of the results, limitations remain. Primary limitation is raised from the retrospective nature and the short length of follow up of the clinical evidence. Multiple trials have examined the ability of oral chelation therapy to lower serum ferritin concentrations. These studies are mostly observational and include both adult and pediatric patients. Which raise doubts about the validity of pooling data taking in the consideration that children and adults are metabolize drugs differently and so efficacy may also differ by age.

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Furthermore, given the chronic nature of iron overload, trials presenting data at 12 months are only able to provide evidence on surrogate, intermediary outcomes and therefore these studies are unable to fully consider important issues around long-term efficacy, safety and adherence. However, to date, no study has been designed to examine the frequency of cardiac complications and survival as the primary outcomes of a comparative study between these two chelators, Deferiprone and Deferasirox.

In addition to the uncertainties associated with the clinical effectiveness, there are methodological issues relating to the nature, derivation and quality of data used to populate the model in general. While, increasing use has been made of Markov models, which allow for the management of patients in and between different health states over time to assess the relative cost effectiveness of different treatments, problems are still too readily apparent. Firstly, the timescales involved frequently extend beyond the duration of clinical trials developed to assess clinical effects, and there is a lack of consensus as to the longer-term effects of ICT.

Secondly, as in all modeling exercises, several assumptions were made in this study leading to uncertainties in the results. This includes the probability of developing cardiac disease, mortality based on published sources. To assess the influences of different assumptions and other model structures on the cost-effectiveness estimates, one-way sensitivity analysis of various parameters were performed as discussed above.

Regarding other published economic analyses, when Deferasirox is compared with Deferiprone it is a less clear-cut picture and depends upon the utility benefit attributed to Deferiprone in relation to Deferasirox. However, given the large price differential between Deferasirox and Deferiprone it is unlikely that Deferasirox will be generally cost-effective for the majority of patients. In the youngest patients, Deferasirox appears to be cost-effective as the lower doses required incur less extra cost; while for older children and adults, Deferiprone appears to be economically more attractive.

However, no studies have attempted to estimate the costs and consequences of adverse events associated with Deferiprone. Given that Deferiprone has been linked with Neutropenia and Agranulocytosis, the costs and dis-utilities associated with Deferiprone complications could make it a non-attractive choice.

A special problem with Egyptian children taking Deferiprone which it's burning taste in addition to being syrup to be taken three times daily. The highest percentage of noncompliance was seen among patients on Deferiprone 7.8%, while 0% in patient on Deferasirox [19]. All these factors are captured in our model would impact upon the cost-effectiveness of Deferiprone and may mean that it is less economically attractive when compared with Deferasirox.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

- **Conclusion**

Results from this study suggest that employing a DFX strategy is cost-effective intervention compared to DFP in Thalassemia young patients with high iron level in the blood, 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.

Our clinical and economic analysis was restricted by the available evidence. To be able to form more robust conclusions, further research is required regarding the long-term benefits of the two chelators in different patient population; the consequences in the long term; the adverse event and adherence profiles. Further steps are required to be adopted locally to validate new diagnostic tools, such as Magnetic Resonance Imaging (MRI) against cardiac iron, and to establish the link between cardiac iron and longer-term outcomes, such as cardiac morbidity and mortality.

- **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:

- **Dr. Gihan Hamdy,** Head of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.
- **Prof. Ahmed Hassouna**, Consultant of clinical trials and biostatistics.
- **Prof. Mahmoud Khattab,** Professor of pharmacology and toxicology, faculty of pharmacy, Cairo University.
- **Prof. Heba Nassar,** Professor at the Faculty of Economics and Political Science, Cairo University.
- **Prof. Amal El-Beshlawy,** Professor of Pediatric Hematology, Cairo University Hospital.
- **Prof. Naglaa Shahin,** Head of pediatric hematology department at Misr Children Hospital.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

- **PEU project team**

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

- **Shaimaa Fouad Ahmed,** Team member of Pharmacoeconomic Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.

- **References:**

1 El-Beshlawy A, Youssry I. Prevention of hemoglobinopathies in Egypt. Hemoglobin.2009; 33(1):S14–S20.
2 Pignatti C, Cappellini MD, De Stefano P, et al. Survival and complications in thalassemia. Ann NY Acad Sci. 2005; 1054:40–47.
3 Pagon RA, Adam MP, Ardinger HH, et al. Beta-Thalassemia Synonyms: Cooley's anemia, Mediterranean Anemia. GeneReviews. Last Update: May 14, 2015
4 Cunningham MJ. Update on Thalassemia: Clinical Care and Complications. Hematol Oncol Clin North Am. 2010;24:215-27
5 Galanello R, Campus S. Deferiprone chelation therapy for thalassemia major. ActaHaematol.2009; 122:155–64.
6 Pennell DJ, Porter JB, Piga A, etal. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in β-thalassemia major (CORDELIA). Blood. 2014; 123:1447–54.
7 Roberts D, Brunskill S, Doree C. Deferiprone for Iron Chelation in People with Thalassemia. Cochrane Database Syst Rev. 2007; 3: CD004839. 7.
8 Meerpohl JJ, Antes G, Rücker G. Deferasirox for managing Transfusional Iron Overload in People with Sickle Cell Disease. Cochrane Database Syst Rev. 2010; 4:CD007477.
9 Pepe A, Meloni A, Capra M, etal. Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison determined by quantitative magnetic resonance imaging. Haematologica. 2011 Jan;96(1):41-7
10 Berdoukas V, Chouliaras G, Moraitis P, etal. The efficacy of iron chelator regimes in reducing cardiac and hepatic iron in patients with thalassaemia major: a clinical observational study. J Cardiovasc Magn Reson. 2009 Jun 28; 11:20.
11 Dimitrios T, Dimitrios F, Athanasios A, etal. β-Thalassemia Cardiomyopathy History, Present Considerations, and Future Perspectives. Circ Heart Fail. 2010; 3:451-458
12 Elsisi G, Kaló Z, Eldessouki R, et al; Guidelines for reporting pharmacoeconomic evaluations in Egypt; Value in Health Regional Issues; Volume 2, Issue 2, September–October 2013, Pages 319–327
13 Piga A, Gaglioti C, Fogliacco E, etal. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica. 2003; 88:489–96.
14 Karnon J, Tolley K, Oyee J, etal. Cost–utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom.Curr Med Res Opin. 2008; 24(6):1609–1621.

15 McLeod C, Fleeman N, Kirkham J, etal. Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation. Health Technol Assess. 2009 Jan; 13(1): iii-iv, ix-xi, 1-121.

16 Bentley A, Gillard S, Spino M, etal. Cost–Utility Analysis of Deferiprone for the Treatment of β-Thalassaemia Patients with Chronic Iron Overload: A UK Perspective. Pharmacoeconomics. 2013 November 5; 31: 1185.

17 GlobalHealthObservatory (http://who.int/gho/mortality_burden_disease/en/) Lastupdated:January2015.

18 Delea TE, Sofrygin O, Thomas SK, etal. Cost Effectiveness of Once-Daily Oral Chelation Therapy with Deferasirox versus Infusional Deferoxamine in Transfusion-Dependent Thalassaemia Patients US Healthcare System Perspective. Pharmacoeconomics. 2007; 25 (4):329-42.

19 Mokhtar GM, Gadallah M, El Sherif NH, etal. Morbidities and mortality in transfusion-dependent Beta-thalassemia patients (single-center experience). Pediatr Hematol Oncol. 2013 Mar; 30(2):93-103.