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## COST EFFECTIVENESS ANALYSIS OF ORAL IRON CHELATING DRUGS BETWEEN DEFERIPRONE AND DEFERASIROX IN THALASSEMIA MAJOR PATIENTS AT BHAYANGKARA SETUKPA LEMDIKLAT POLRI TK.II HOSPITAL

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### ABSTRACT

Thalassemia is a blood disorder that results from decreased or lost synthesis of one or more globin chains. Thalassemia major as a red blood cell disorder requires high costs because it requires blood transfusions and the use of iron chelation drugs throughout the patient's life. This study aims to analyze the cost and effectiveness of oral iron chelation drugs such as deferasirox and deferiprone in patients with Thalassemia major at Setukpa Lemdiklat Polri Tk—II Hospital in 2023. Data was collected retrospectively using total sampling from patient medical records and hospital information system data. Based on the results of this study, the average total cost per treatment for thalassemia major patients who used deferasirox (IDR 52,969,775,-) was more expensive than deferiprone (IDR 49,407,613,-). The effectiveness of deferasirox (1,364 ng/mL) was bigger than that of deferiprone (1,210 ng/mL). The cost-effectiveness ratio of deferasirox (IDR 38,834,-) was lower than that of deferiprone (IDR 40,833,-). To change the drug from deferiprone to deferasirox requires an additional cost of IDR 23,130 per one additional unit. From the average cost-effectiveness ratio, it can be concluded that deferasirox is more cost-effective than deferiprone.

**Keywords:** thalassemia major, cost effectiveness analysis, oral iron chelating drugs, deferiprone, deferasirox

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### INTRODUCTION

Thalassemia is a blood disorder that is a hereditary disease inherited from parents to children and is characterized by decreased or absent normal globin chain synthesis. This disease has several types, and the most common type of thalassemia is beta thalassemia major, which is at 50% (A. B. M. K. Nisa et al., 2023). Thalassemia sufferers need periodic blood transfusions to maintain normal hemoglobin levels (Jin et al., 2023). However, ironically, the amount of iron accumulated in the body due to transfusion can be the cause of death (Yula et al., 2021).

Therefore, iron chelation therapy is needed to prevent complications in other organs (Geneen et al., 2023).

The number of sufferers of thalassemia in Indonesia is still relatively high (Widyastiti et al., 2023). According to data, 10,531 patients were detected as suffering from Thalassemia Major (Dasauni et al., 2021). Meanwhile, as many as 2,500 newborn babies are predicted to carry thalassemia every year (Fatkuriyah & Hidayati, 2022). Treatment for thalassemia has not yet reached the healing stage (Cappellini et al., 2018). Throughout the world, the protocol for treating thalassemia is symptomatic in the form of lifelong blood transfusions.

The need for one thalassemia major patient weighing 20 kilograms for adequate blood transfusion and iron chelation can cost around 300 million rupiah per year. This amount does not include laboratory and monitoring costs and management of complications that may arise (F. A. Nisa, 2023). Iron chelating drugs are important for all patients who receive repeat Packed Red Cell (PRC) transfusions to remove excess iron from chronic anemia, and the main management protocol (PRC transfusion) is given (Ansari et al., 2007).

One 250 ml bag of blood contains around 200 mg Fe, while the iron/Fe that can exit the human body is only 1-3 mg/day. This excess iron will accumulate in all organs, including the liver, heart, and hormone-forming glands (Shashkova, n.d.). Currently, in Indonesia, there are three types of iron-chelating drugs available, namely deferoxamine, which is given subcutaneously, deferiprone, and deferasirox, which is given orally.

Deferiprone and deferasirox are more often used in hospitals because they are not cheaper, and the level of compliance is higher than deferoxamine (Gatot et al., 2007); (Salem et al., 2023). Apart from that, Deferiprone and Defarasirox have several differences, both in terms of pharmacokinetics, and side effects produced, although both have good effectiveness in reducing the amount of iron and also different prices as stated on the government e-catalog site which guides BPJS pricing (Utari, 2022).

Defarasirox is slightly more expensive than deferipron (Chairunnisa et al., 2018); (Kontoghiorghe & Kontoghiorghes, 2016); (Viprakasit et al., 2023). Financing for iron chelation medicine in the National Health Insurance (JKN) era is implemented using a top-up package system where whatever the cost of iron chelation medicine issued by the hospital to the patient, the value of the package paid by BPJS is determined (Rahayu, 2019). Hospitals must consider selecting efficient and effective drugs (cost-effectiveness).

Bhayangkara Hospital Kindergarten. II Setukpa Lemdiklat Polri is one of the referral hospitals for treating thalassemia sufferers from 3 districts/cities, namely Sukabumi City, Kab. Sukabumi, and Kab. Cianjur, with more than 200 patients, uses iron chelation drugs as the highest-cost component in therapy for thalassemia sufferers. At Bhayangkara Hospital Kindergarten. II Setukpa Lemdiklat Polri Iron chelating drugs are available, namely deferipron and deferasirox. Researchers want to know which drugs are more effective and cost-efficient.

## RESEARCH METHODS

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This research is a non-experimental observational cross-sectional study with retrospective data collection (Gonzalez-Aguines et al., 2023). The identification step begins by looking at and recording the flow of Thalassemia patient activities and being able to determine

what costs are involved in treating thalassemia patients, for example, drug costs, administration costs, hospitalization costs, medical equipment costs, blood bag costs, laboratory costs, and so on. Data collection was carried out retrospectively (Eftekhari et al., 2023). Data collection is done by recording all activities related to the variables studied during the research period. The data collected is secondary data from various sources: patient medical records, pharmaceutical installations, laboratory installations, financial departments, and data tracing in other units for related research purposes.

The study population was all thalassemia patients from January 2023 to December 2023. Data collection used a purposive sampling technique, namely selecting sampling units that met the inclusion and exclusion criteria to obtain a sampling that had the desired characteristics. The research was conducted at Bhayangkara Tk Hospital. II Setukpa Lemdiklat Polri, Sukabumi, from October 2023 to January 2024.

## RESULTS AND DISCUSSION

### General Description of Research Population and Sample

This research conducted a cost-effectiveness analysis of oral iron chelation drugs between Dederipron and Deferasiroks in thalassemia major patients at Bhayangkara Tk Hospital. II Setukpa Lemdiklat Polri Data from thalassemia patients from January 2023 to December 2023 was 168. 141 patients met the inclusion criteria, and 27 patients met the exclusion criteria. Based on the data that has been taken, samples are then grouped that meet the inclusion and exclusion criteria as follows:

**Table 1. Sample Grouping**

Sample Criteria	Amount
Fulfills inclusion criteria:	
Getting Deferiprone Therapy	75
Get Deferasirox therapy	66
Fulfills inclusion criteria:	
Obtaining injectable iron chelation medication	0
Obtaining a combination oral iron chelator	0
Had a change to iron chelation medication	8
Suffering from liver or kidney dysfunction	0
Suffering from metabolite syndrome	2
Stopped getting iron chelation medication	13
Stopped getting a blood transfusion	3
Amount	168

Henceforth, data was collected on patients who met the inclusion criteria, namely 75 patients who received Deferipron therapy and 66 patients who received Deferasirox therapy. Patient criteria based on the age of the research sample are as follows:

**Table 2. Patient Criteria Data Based on Age**

Age Group	Getting Deferiprone Therapy		Getting Deferasirox Therapy	
	Amount	Percent (%)	Amount	Percent (%)
<b>Child Criteria:</b>				
Age 0 – 5 years	5	6,7	1	1,5
Age ≥ 5 - ≤ 10 years	30	40,0	11	16,7
Age ≥ 10 - ≤ 15 years	15	20,0	28	42,4
Age ≥ 15 - ≤ 19 years	16	21,3	15	22,7
<b>Amount</b>	<b>66</b>	<b>88,0</b>	<b>55</b>	<b>83,3</b>
<b>Adult Criteria:</b>				
Age ≥ 19 - ≤ 25 years	7	9,3	6	9,1
Age ≥ 25 - ≤ 30 years	4	5,3	2	3,0
Age ≥ 35 - ≤ 40 years	2	2,7	2	3,0
Age ≥ 40 years	1	1,3	1	1,5
<b>Amount</b>	<b>14</b>	<b>12,0</b>	<b>11</b>	<b>16,7</b>
<b>Total number</b>	<b>75</b>	<b>100,0</b>	<b>66</b>	<b>100,0</b>
<b>Average Age (years)</b>	<b>12,9</b>		<b>14,7</b>	

From Table 2, it can be seen that the majority of patients involved in this study were children, namely 88.0% with an average age of 12.9 years for those who received deferiprone iron chelation therapy and 83.3% with an average age of 14.7 years for those receiving deferasirox therapy. Patient criteria based on gender are as follows:

**Table 3. Patient Criteria Data Based on Gender**

Gender	Getting Deferiprone Therapy		Getting Deferasirox Therapy	
	Amount	Percent (%)	Amount	Percent (%)
Male	35	46,7	34	51,5
Female	40	53,3	32	48,5
<b>Amount</b>	<b>75</b>	<b>100</b>	<b>66</b>	<b>100</b>

Table 3. shows that the gender involved in this study was different among those who received iron chelation therapy. Namely, 46.7% of male and 53.3% of female received

deferiprone iron chelation therapy, and 51.5% of male and 48.5% of female received deferasirox therapy.

### **Pharmacoeconomic Analysis**

According to information from The New Oxford American Dictionary, opportunity loss is the loss of profit, which can result from one choice or alternative because the decision maker chooses to use another option/alternative. Drugs with output/output/effectiveness better than standard drugs are only useful if reasonably priced. In economics, resources (for example, money) are always limited. Therefore, payers must appropriately budget limited funds to choose a drug that produces the greatest benefit.

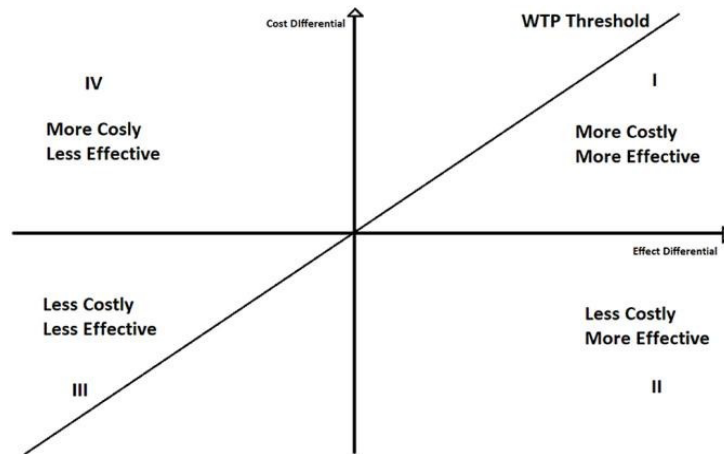
Comparison of costs and therapeutic output between at least two drug alternatives can be plotted on a two-dimensional image, often referred to as the Cost Effectiveness Plane (CEP). The cost and effectiveness of therapy from the emergence of new drugs, when compared with existing drugs, can be divided into 4 possibilities, namely:

Quadrant (i): new drugs have higher effectiveness and higher costs than existing drugs (higher effectiveness and higher cost). This requires pharmacoeconomic studies to determine whether new drugs are acceptable in health care. Here, deferasirox occupies quadrant (i) in terms of cost. It can be seen that using 1 deferasirox tablet/day is worth Rp. 81,400,- (Kalsirox 500 brand) or Rp. 63,825,- (Dextron 500 brand), is higher than 3 deferipron tablets/day worth Rp. 49,950,- (Oferlod brand). According to research by Asti Y. Rindarwati, Ajeng Diantini, and Keri Lestari (2016), deferasiroks are more effective than deferipron based on reducing serum ferritin levels.

Quadrant (ii): new drugs have better effectiveness but cheaper costs (higher and lower effectiveness). This does not require a pharmacoeconomic study because the new drug should be acceptable in health services.

Quadrant (iii): new drugs have lower effectiveness and cheaper costs (lower effectiveness and lower cost). This requires pharmacoeconomic studies such as quadrant (i). Deferipron is in this quadrant, requiring the same pharmacoeconomic study as deferasirox in quadrant (i).

Quadrant (iv): new drugs have lower effectiveness and higher costs (lower effectiveness and higher costs). New drugs in this position certainly do not need to be used in the health care system.



**Figure 1. Cost Effectiveness Plane (CEP) of new drugs**

The cost component that is the object of research is direct medical costs taken from Hospital Information System (SIM-RS) data by searching using the medical record numbers of thalassaemia major patients who meet the inclusion criteria in the study. Direct medical costs are related to health services, including drug costs (and health supplies), doctor consultation costs, nursing service costs, use of hospital facilities (inpatient rooms, equipment), laboratory examinations, informal service costs, and other health costs. Apart from medical costs, in direct medical costs, non-medical costs such as ambulance costs and other patient transportation costs are often considered (Ministry of Health, 2013).

**Table 4. Description of direct medical costs for thalassaemia patients at Bhayangkara TK Hospital. II Setukpa in 2023**

Cost component	Unit	Price
Specialist Doctor Visit (per visit)	Package	Rp 70.000,-
Nursing Care (per visit)	Package	Rp 100.000,-
Laboratory examination :		
Routine Blood: Hb, Leukocytes, Platelets and Hematotrites (per visit)	Package	Rp 52.000,-
SGOT (per visit)	Package	Rp 23.000,-
SGPT (per visit)		Rp 23.000,-

Current Blood Sugar (per visit)	Package	Rp	23.000,-
Ureum (once 3 months)	Package	Rp	23.000,-
Creatinine (every 3 months)	Package	Rp	23.000,-
Ferritin (once 6 months)	Package	Rp	237.000,-
PRC blood flask (per visit)	flask	Rp	360.000,-
Medical equipment and transfusion medication (per visit)	Package	Rp	50.000,-
Iron chelation drugs:			
Oferlod 500 mg (deferiprone) per month	Tablet	Rp	16.650,-
Ferriprox syr (deferiprone) per month	Bottle	Rp	1.286.163,-
Calsirox 500 mg (deferasirox) per month	Tablet	Rp	81.400,-
Dextron 500 mg (deferasirox) per month	Tablet	Rp	63.825,-
Supplements:			
Folic Acid (monthly)	Tablet	Rp	200,-
Santa E (Vitamin E 100 IU) per month)	Tablet	Rp	1.166,-
Other medications (according to diagnosis)	-	-	

Based on Table 4, it shows an overview of the costs incurred in treating thalassemia patients in the smallest units. The many cost components illustrate the complexity of treating thalassemia patients according to the therapy protocol for managing thalassemia patients.

**Table 5. Realization of direct medical costs for thalassemia patients at Bhayangkara TK Hospital. II Setukpa in 2023**

Cost component	Unit	Amount	Price
Visit a Specialist Doctor	Package	2.936	Rp 205.520.000,-
Nursing care	Package	2.936	Rp 293.600.000,-
Laboratory examination :			

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Routine Blood	Package	2.936	Rp	152.672.000,-
	Package			
SGOT	Package	2.936	Rp	67.528.000,-
SGPT		2.936	Rp	67.528.000,-
When blood sugar	Package	2.936	Rp	67.528.000,-
Urea	Package	672	Rp	15.456.000,-
Creatine	Package	672	Rp	15.456.000,-
Ferritin	Package	336	Rp	79.632.000,-
Sub-Total :			Rp	465.800.000,-
PRC blood flask	flask	3.804	Rp	1.369.440.000,-
Medical devices and transfusion medicine	Package	2.936	Rp	146.000.000,-
Iron chelation drugs:				
Oferlod 500 mg	Tablet	26.080	Rp	434.232.000,-
Ferriprox syr	Bottle	587	Rp	770.113.765,-
Calcirox 500 mg	Tablet	9.886	Rp	797.765.200,-
Dextron 500 mg	Tablet	4.363	Rp	278.468.475,-
Sub-Total :			Rp	2.280.579.440,-
Supplements:				
Folic acid	Tablet	25.680	Rp	5.136.000,-
Santa E 100 IU	Tablet	25.680	Rp	29.802,960,-
Sub-Total :			Rp	29.802.960,-
Medicines and other medical equipment	-	-	Rp	62.398.123,-
Amount			Rp	4.348.156.514,-

Based on Table 5, it shows that the biggest cost in treating thalassemia patients at the Bhayangkara Tk.II Setukpa Lemdiklat Polri Hospital is the cost of chelation medication amounting to IDR 2,280,579,440,- far exceeding the cost of blood flasks amounting to IDR 1,369,440,000,-, this shows that the treatment Iron chelation therapy is a high-cost therapy with a total realized cost of IDR 4,348,156,514,-

The results of CEA are described as a cost and effectiveness ratio (C/E ratio), the numerator of the ratio shows the total costs, and the denominator of the ratio describes the effectiveness/output variable. So it is presented in terms of cost to effect, or it can be formulated:

$$ACER = \frac{\text{Total average cost of an episode of care}}{\text{Average drug effectiveness}}$$

**Figure 2. Average Cost Effectiveness Ratio (ACER) formula**

**Table 6. Results of ACER calculations using the drugs deferiprone and deferasirox**

No	Medicine name	Average total cost per episode of care	Average effectiveness of reducing levels serum ferritin	ACER
1.	Deferiprone	49.407.613	1.210	40.833
2.	Deferasirox	52.969.775	1.364	38.834

From the stages of calculating the cost effectiveness between the drugs deferasirox and deferiprone using the ACER formula, the ACER for patients who use the drug deferiprone is IDR 40,833,-, while the ACER value for patients who use the drug deferasirox is IDR 38,834,-. From this research, it was concluded that the drug deferasirox is more cost-effective than deferiprone. Next, it is necessary to determine each drug's position to define "cost-effectiveness."

**Calculation of Incremental Cost Effectiveness Ratio (ICER)**

There are three possibilities for a new drug to be compared: more expensive but more effective (cell I), cheaper but less effective (cell A), or with the same cost and effectiveness as a standard drug (cell E). Because the drugs deferasirox and deferiprone are in cells I and A, it is necessary to determine the ICER value to determine the additional costs for each additional unit of outcome.

$$ICER = \Delta C / \Delta E = (\text{Cost treatment A} - \text{Cost treatment B}) / (\text{Effect treatment A} - \text{Effect treatment B})$$

$$ICER = \Delta C / \Delta E = (\text{Cost of Deferasirox} - \text{Cost of eferiprone}) / (\text{Effectiveness of Deferasirox} - \text{Effectiveness of Deferiprone})$$

$$ICER = \Delta C / \Delta E = (52.969.775 - 49.407.613) / (1.364 - 1.210)$$

$$ICER = \Delta C / \Delta E = 3.562.162 / 154$$

$$ICER = \Delta C / \Delta E = 23.130$$

The *ICER* value is determined to determine the additional costs for each increase in the effectiveness of a drug. The *ICER* value obtained is IDR 23,130 per effectiveness. The *ICER* value shows that additional costs are required if therapy is to be switched from deferiprone to deferasirox. In other words, if a hospital needs to increase the effectiveness of treatment using deferasirox, then the hospital must incur additional costs of IDR 23,130 per effectiveness. The effectiveness of deferasirox is greater than deferiprone, but the costs required to use the drug deferasirox are also greater. Hospitals must consider whether a budget policy is needed if funding problems are found in using the drug deferasirox.

The aspect of uncertainty (uncertainty) of various data used or produced (including due to lack of data availability, study results in the form of temporary averages in reality randomly distributed values within a certain range, or generalization of study results, causes the impact of elements of uncertainty to be identified, assessed, and interpreted primarily for the parameters that are most dominant in the study results. In this study, one-way sensitivity analysis was carried out by changing the value of a variable within a possible range while keeping the values of other variables constant. Sensitivity analysis can be seen in Table 7 as follows:

**Table 7. Sensitivity analysis of deferiprone and deferasirox in thalassemia major patients**

Sensitivitas	Cost (A)	Until the decline serum ferritin (B)	ACER (A/B)
<b>Deferiprone</b>			
Baseline values	49.407.613	1.210	40.833
25% decrease	37.055.709	1.210	30.624
25% increase	61.759.516	1.210	51.041
<b>Deferasirox</b>			
Baseline values	52.969.775	1.364	38.834
25% decrease	39.727.331	1.364	29.126
25% increase	66.212.219	1.364	48.543

Sensitivity analysis showed that the selection of deferasirox was sensitive to a 25% increase in costs, where the ACER value of deferasirox would be higher than the baseline deferiprone. The choice of deferasirox is also sensitive to a 25% cost reduction in deferiprone where the ACER value of deferiprone will be lower than the baseline ACER value of deferiprone. The lower ACER value of deferasirox with a better reduction in serum ferritin levels makes deferasirox more cost-effective.

## CONCLUSION

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Based on the research that has been carried out, it can be concluded as follows: The average total cost per treatment episode for thalassemia major patients who use the drug deferiprone is Rp. 49,407,613,-, The total cost per treatment episode for thalassemia major patients using Defasirox is Rp. 52,969,775,-. The effectiveness of drug use in thalassemia major patients who use the drug deferiprone is 1,210 ng/mL. The effectiveness of drug use in thalassemia major patients who use the drug deferasirox is 1,364 ng/mL. The costs incurred are compared with the effectiveness (cost-effectiveness ratio) of deferipron in thalassemia major patients at Bhayangkara Tk Hospital. Il Setukpa Polri is Rp. 40,833,-, The costs incurred are compared with deferasirox's effectiveness (cost-effectiveness ratio) in thalassemia major patients at Bhayangkara Tk Hospital. Il Setukpa Polri is Rp. 38,834,-, From the ACER value, it was concluded that deferasirox was more cost-effective than deferiprone. From the ICER value, if a hospital needs to increase effectiveness by switching treatment from deferiprone to deferasirox, then it must incur additional costs of IDR 23,130 per effectiveness Indonesia has many ICT-related regulations and the acceleration of digital transformation, including laws and presidential regulations, financial institution regulations, ministerial regulations, and ministerial circulars.

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