ORIGINAL ARTICLE

Budget Impact Analysis of Ferric Derisomaltose for the Treatment of Iron-Deficiency in Malaysia

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ABSTRACT

Introduction: Untreated iron deficiency (ID) can lead to severe anaemia, requiring blood transfusion, or increased mortality risk. Globally intravenous (IV) iron is increasingly recognised as a recommended option for patients. This study aims to evaluate the budget impact associated with introducing a new intravenous (IV) iron, ferric derisomaltose (Monofer® [IIM]) as one of the treatment options for the management of ID in the Ministry of Health Malaysia (MOHM) setting. **Methods:** A 5-year budget impact model was developed from 2020 to 2024 for patients with ID that require a high iron dose (≥500 mg), using the perspective of MOHM. The model was built with four external medical specialists, each with experience and deep knowledge of ID management, to support estimations on the future development of iron use in Malaysia. **Results:** Compared to the current market mix with the existing IV iron products (i.e., iron sucrose and iron dextran), a cost-saving of MYR 53,910 could be achieved with the introduction of IIM in 2020. The uptake of IIM into MOHM over five years is estimated to lead to an overall budget saving of MYR 11,837,524 over a 5-year time horizon. **Conclusion:** The use of IIM in place of the current IV iron products in MOHM resulted in a significant cost saving by reducing the number of visits required to achieve the targeted iron dose and the shorter IV infusion time with IIM.
Malaysian Journal of Medicine and Health Sciences (2023) 19(4):110-116. doi:10.47836/mjmhs19.4.17

Keywords: Saccharated ferric oxide, Ferric derisomaltose, Cost savings, Iron deficiencies, Anaemia

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INTRODUCTION

In humans, haemoglobin is the most prevalent iron-containing protein. Despite the abundance of iron on earth, iron deficiency (ID) is widespread among humans and the leading cause of anaemia worldwide. Iron deficiency anaemia (IDA) occurs when the balance of iron intake, iron reserves and iron loss in the body is insufficient to sustain erythrocyte synthesis. Although IDA seldom results in death, it substantially influences human health. This disease is easily detected and treated in the developed world but can be frequently neglected by clinicians. In contrast, it is a public health issue that affects a large population in developing countries. Intravenous (IV) iron is increasingly recognised as a viable treatment for patients failing to respond to oral iron, having concomitant diseases that may limit oral iron effectiveness or requiring repletion in a short period (i.e., impaired oral iron absorption in the period of fewer than six weeks to major surgery or the third trimester of pregnancy).

It is estimated that approximately 200-250 mg iron is required to increase Hb by 1 g/dL (if anaemic), and 8mg iron equates to approximately 1 ng/mL of serum ferritin (1). Only serum ferritin values greater than 100ng/mL confirm the full treatment of ID (2). As such, it can be conferred that most patients with iron deficiency anaemia (IDA) will require at least 1,000 mg of iron to correct their deficiency.

The 2021 UK National Institute for Health and Care Excellence (NICE) guideline recommends considering high-dose, low-frequency IV iron as the treatment of choice for adults and young people with IDA not receiving haemodialysis (3). Similar guidelines and expert consensus statements exist for therapeutic areas such as chronic heart failure (4), inflammatory bowel disease (5), oncology (6), obstetrics & gynaecology (7,8) and pre/post-surgery (9,10) (often referred to as patient blood management or PBM).

For PBM, to minimise the risk of transfusions, outpatient preoperative treatment is recommended using parenteral iron when clinically indicated (9,11) and in post-operative settings, the use of high-dose agents permitting a single infusion is indicated in the recent International Consensus Statement (10). This is a crucial aspect as a driver of future IV iron use in Malaysia due to the high volume of RBC transfusions performed annually combined with the limited supply of blood and the correspondingly high costs associated with collecting and administering blood products. Two recent extensive studies from Germany and the UK have demonstrated that leaving patients untreated with ID with or without concomitant anaemia correlates to increased mortality – with absolute ID patients (defined as serum ferritin <30 ng/mL) having a 90% increased risk of death over 10 years (12,13).

Due to the resultant anaemia combined with other known and emerging conditions correlating with untreated ID combined with the increased efficacy and improved safety of new generation IV irons, such as ferric derisomaltose, formerly known as iron isomaltoside (Monofer® [IIM], Pharmacosmos A/S), the implementation and adoption of IV iron into routine medical practice is expected to increase. International experts encourage physicians to consider prioritising IV iron, rather than oral iron, as a treatment for ID in some clinical scenarios, including in the Ministry of Health Malaysia (MOHM) settings (14).

The currently approved IV products in Malaysia include iron sucrose (Venofer® [IS], Vifor France SA, Victor, France) and low molecular-weight iron dextran, commonly known as iron dextran (Cosmofer® [LMWID], Pharmacosmos A/S, Holbaek, Denmark). The time to infuse these maximal doses is 4-6 hours and over 3.5 hours for LMWID and IS. These long durations make routine administration impractical, especially among outpatients. This study aims to determine the economic impact of introducing IIM as one of the treatment options for managing ID among Malaysian patients using a budget impact model.

MATERIALS AND METHODS

Study design and setting

The budget impact analysis evaluated the cost of using IV iron products available in Malaysia among ID adults. The model was developed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), undertaking the perspective of the MOHM. The interventions included 500 mg and 1,000 mg IIM compared with 100 mg, 200 mg and 500 mg IS, and 100 mg, 200 mg, 500 mg and 1,000 mg LMWID. A 5-year time horizon from 2020 to 2024 was employed. According to the Pharmacoeconomics Guideline for Malaysia, all costs were not discounted and were reported in Malaysian Ringgit (MYR) (15).

As several estimations were required to develop this model, four expert clinicians with vast experience in using high-dose IV iron were engaged in the expert advisory panel: a government hospital haematologist, a private hospital transfusion specialist, a university hospital anaesthetist and a private hospital nephrologist. The study population is ID adults with an average Malaysian body weight of 62.25 kg (16). A bottom-up approach was undertaken to estimate the targeted population size using the volume use of each iron product in the MOHM setting.

To estimate the number of eligible patients for IV iron, the iron usage per year (100 mg equivalent) in the MOHM setting was divided by the average dose per patient per year. The annual iron usage in 100 mg equivalent over a 5-year time horizon from 2020 to 2024 was projected using the annual growth of iron usage (iron sucrose and iron dextran) and the actual MOHM iron usage in 2019 obtained from various distributors and an established medicine price data provider (IQVIA Malaysia, Petaling Jaya, Malaysia). The annual growth of iron use was forecasted based on the growth observed in other markets. The estimated average iron dose between 700 mg in 2020 to 1,000 mg in 2022 was used to reflect the change in managing ID in patients with IV iron and the increased medical rationale for iron use (14). Iron usage was calculated based on the annual growth and data of iron usage from distributors and IQVIA 2017-2019 (Table I). Although the calculated required iron dose for ID is often above 1,000 mg using the Ganzoni calculated dose (17) and simplified dose regimen (18) formula, the model limits an average of 1,000 mg iron per patient per year in line with the routine practice of the product and resource limitations. Thus, the number of eligible patients receiving IV iron was estimated to be 40,058 in 2020 to 76,656 in 2024. As IIM permits

Table I: Iron usage and population size estimation

Parameters	Year					Source
	2020	2021	2022	2023	2024	
Iron usage growth (%)	25	35	35	25	20	Forecasted
Iron usage (100mg equivalence)						Calculated
Iron sucrose	8,412	18,927	40,883	76,656	153,312	
Iron dextran	71,994	359,621	470,157	562,144	613,248	
Total	280,406	378,548	511,040	638,800	766,561	
Estimated average dose per patient (mg)	700	850	1,000	1,000	1,000	Expert Advisory Panel
Estimated number of patients	40,058	44,535	51,104	63,880	76,656	Calculated

the delivery of high iron doses in a single infusion in a short time, the calculated population size is adjusted to consider only those requiring high iron doses (≥ 500 mg) in the model.

Market mix

The current market mix consists of the existing IV iron products available in MOHM, while IIM is not currently listed in MOHM as a treatment option. The IV iron products currently listed in the MOHM are: (i) IS 5x5 mL (5 mL is equivalent to 100 mg iron) administered in doses of up to 500mg of iron over 3.5 hours; (ii) LMWID 5x2 mL (2 mL is equivalent to 100 mg iron) administered up to 20 mg/kg over a 4-6 hour post-applicable test dose. For both products above, the most common dosing options are 100, 200 and 500 mg of iron in a single administration. IS is occasionally administered at doses of 1,000 mg of iron. The annual market share of IS was estimated based on the growth of sucrose copies introduced to the market (Table II).

As for the alternative market mix, IIM has two vial strengths, 5 mL (500 mg iron) and 10 mL (1,000 mg iron), available in Malaysia. Dosing is permitted up to 20 mg iron per kg with doses of up to 1,000 mg in under 15 minutes and doses >1,000 mg in under 30 minutes. The projected market share of the currently available iron products was based on their historical growth combined with opinions from the expert advisory panel. On the other hand, the projected uptake of IIM in the alternative market mix was estimated based on the expert advisory panel.

Given that the model considers those requiring a high iron dose (≥ 500 mg) only, it assumes that patients with low iron doses (< 500 mg) continue to be treated with existing iron products, namely iron sucrose and iron dextran. Based on an estimated 15% annual increase in low iron dose, the annual iron usage indicated for high iron dose was estimated to increase from 99,825 mg in 2020 to 450,772 mg in 2024, corresponding to the change in practice for managing ID and anaemia with IV iron.

To derive the number of high-dose patients per iron product in different strengths, the total volume per iron product for high dose was apportioned to estimate the annual usage of each iron product in different strengths. Subsequently, this was divided by the average iron dose per patient per year. The proportion of each iron product usage in different strengths was assumed to be constant in both scenarios throughout the 5-year time horizon: IS 100 mg: 20%, 200 mg: 75%, and 500 mg: 5%; LMWID 100 mg: 20%, 200 mg: 60%, 500 mg: 15%, and 1,000 mg: 5%; IIM 500 mg: 10% and 1,000 mg: 90%. As a result, the number of patients requiring high iron doses was estimated to be 14,261 in 2020 to 45,072 in 2024.

Input cost data

As the model assumes equal efficacy and safety per gram of iron among all iron products (14), only cost inputs were populated. Two cost categories were included: the cost of each iron product and treatment cost during IV iron infusion. All cost inputs were expressed in the 2019 Malaysian Ringgit (MYR) values.

The cost of the iron product was calculated using the unit cost of each iron product and the number of visits required to achieve the average iron dose per patient per year. All doses of the iron products were based on the National Pharmaceutical Regulatory Agency (NPRA) approved product labels. An additional cost associated with a test dose was included for LMWID.

Considering that patients were required to visit a daycare centre or a hospital to receive an IV iron infusion, the treatment cost of each iron dose was derived using the time cost associated with clinicians and nurses during the administration of IV iron infusion and the clinic cost. It was assumed that at each visit, a clinician spent 20 minutes on consultation (at the first dose only), 10 minutes on IV cannula insertion and 20 minutes on patient discharge. A nurse spent 30 minutes on test dose administration (if any), variable IV infusion time ranging from 2 to 360 minutes depending on the iron product used, and 30 minutes post-infusion monitoring.

Resources used in the clinic were calculated based on the total time of patients occupying a hospital bed (19), including the time taken for cannulation and total infusion time, the number of cannulation kits, saline packs used during their infusions, and other miscellaneous products. All administration times of the iron products were based on the Malaysian National Pharmaceutical Regulatory Agency (NPRA) approved product labels. The unit cost of clinician (20) and nurse (21) time was obtained from

Table II: Market share of IV iron products in different market mix scenarios

Annual market share (%)	Year					Source/Remark
	2020	2021	2022	2023	2024	
Current market mix						
Iron sucrose	3	5	8	12	20	Estimated
Iron dextran	97	95	92	88	80	Calculated
Alternative market mix						
Iron sucrose	3	5	8	12	20	Estimated
Iron dextran	95	85	70	45	35	Estimated
Ferric derisomaltose	2	10	22	43	45	Estimated

the average time cost across all specialities. Outpatient bed costs and consumables costs such as cannulation kits, saline, and other miscellaneous products were based on various suppliers. To calculate the total cost of IV iron, the cost per visit including the iron product used and its associated treatment was multiplied by the number of visits required to achieve the target iron dose per year.

Data analysis

In the base-case analysis, the expected budget impact of IIM was calculated as the difference in direct medical costs between the two market mix scenarios. The budget impact outcome was reported in terms of total cost per year. Sensitivity analysis was performed by varying (i) the population size (± 10%), (ii) the market share of iron products in the alternative market mix as in Table III, and (iii) resource use and cost per hour (± 10%).

RESULTS

Based on an eligible patient population of 14,261 adult patients receiving high iron doses in 2020, the base-year cost was estimated to be MYR 9,359,521 in the current market mix compared with MYR 9,305,611 in the alternative market mix. A cost-saving of MYR 53,910 resulted from the introduction of IIM in 2020. Thus, the increased use of IIM is expected to generate an overall budget savings of MYR 11,837,524 over 5 years (Table IV). With the introduction of IIM, the treatment cost associated with the delivery of IV iron was estimated to reduce from MYR 7,469,052 to MYR 7,347,161 in 2020. Fig. 1 summarises the incremental cost difference between two market mix scenarios.

From the sensitivity analysis findings, the time healthcare staff spent on iron administration and the annual market share of each iron product in the alternative market mix were the key drivers that impacted the five-year cost savings with IIM uptake. When the time spent by a clinician and a nurse varied between 75% to 125%, the cost-saving was expected to range from MYR 5,696,007 to MYR 17,979,041, whereas the cost savings associated with IIM was expected to vary with the forecasted market share of IIM, from MYR 5,000,897 in Scenario 1 with a lower market share to MYR 14,522,310 in Scenario 2 with a higher market share (Table V). Considerable changes in the five-year cost-savings following IIM uptake were noted with the ±25% variation in the cost per hour of a clinician and a nurse.

Table III: Annual market share of iron products in the alternative market mix used in the sensitivity analysis

Annual market share of iron products in the alternative market share (%)	Year				
	2020	2021	2022	2023	2024
Scenario 1					
Iron sucrose	3	5	8	12	20
Iron dextran	96	92	85	75	55
Ferric derisomaltose	1	3	7	13	25
Scenario 2					
Iron sucrose	3	5	8	12	20
Iron dextran	95	85	65	40	20
Ferric derisomaltose	2	10	27	48	60

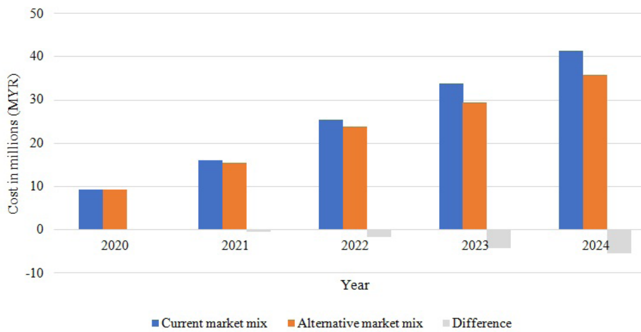

Figure 1: Total cost and incremental differences by year between two market mix scenarios from 2020 to 2024

Table IV: Total cost and difference between two market mix scenarios per year

Cost per year (MYR)	Year				
	2020	2021	2022	2023	2024
Total cost					
Current market mix	9,359,521	15,978,742	25,352,645	33,732,291	41,298,510
Alternative market mix	9,305,611	15,517,324	23,735,501	29,504,020	35,821,729
Difference	-53,910	-461,418	-1,617,144	-4,228,271	-5,476,782
Five-year incremental cost					-11,837,524
Breakdown of the total cost					
Direct iron product cost					
Current market mix	1,890,469	3,229,026	5,127,123	6,828,553	8,377,123
Alternative market mix	1,958,449	3,810,871	7,166,332	12,160,378	15,283,314
Difference	67,981	581,845	2,039,209	5,331,825	6,906,191
Treatment cost					
Current market mix	7,469,052	12,749,716	20,225,522	26,903,738	32,921,388
Alternative market mix	7,347,161	11,706,454	16,569,169	17,343,642	20,538,415
Difference	-121,891	-1,043,262	-3,656,353	-9,560,096	-12,382,973

Table V: Total cost over five years and five-year incremental cost between current and alternative market mix scenarios

Analysis	Current market mix (MYR over 5 years)	Alternative market mix (MYR over 5 years)	Incremental difference (MYR)
Base case	125,721,709	113,884,185	- 11,837,524
Population size			
-10%	113,149,538	102,495,767	- 10,653,771
+10%	138,293,880	125,272,604	- 13,021,276
Market share			
Scenario 1	125,721,709	120,720,812	- 5,000,897
Scenario 2	125,721,709	111,199,399	- 14,522,310
Time spent by healthcare staff			
-25%	102,821,968	97,125,961	- 5,696,007
+25%	148,621,450	130,642,409	- 17,979,041
Cost per hour of a clinician			
-25%	114,373,771	105,098,066	- 9,275,704
+25%	137,069,647	122,670,304	- 14,399,343
Cost per hour of a nurse			
-25%	116,663,963	107,643,619	- 9,020,344
+25%	134,779,455	120,124,752	- 14,654,703
Cost per hour of an outpatient bed			
-25%	123,227,652	112,152,647	- 11,075,006
+25%	128,215,765	115,615,724	- 12,600,042
Cost of clinic resource			
-25%	123,554,096	112,266,199	- 11,287,897
+25%	127,889,322	115,502,172	- 12,387,150

DISCUSSION

IIM is a new generation IV iron with a novel structure that enables tightly bound iron to be administered in doses of up to 20 mg/kg in under 1 hour. It consists of iron and a carbohydrate moiety where the iron is tightly bound in a matrix structure, enabling a controlled and slow release of iron to iron-binding proteins. This minimises the potential toxicity from the release of labile iron. The strongly bound iron within the iron isomaltoside formulation allows flexible dosing, including high dosing (single doses of 1,000 – 2,000 mg) over a short period (22,23).

The cost reduction of using IIM was attributed to delivering a high iron dose in a shorter IV infusion time and fewer visits to achieve the targeted iron dose with IIM. Although there was an increase in the total cost of iron products with the introduction of IIM, the cost reduction associated with treatment cost was large enough to offset the higher iron product cost.

Iron replacement therapies that permit administration in a single visit offer optimal convenience and improved pharmacoeconomics for both patients (less disruption of life, less time away from home/work, reduced injection numbers, lower exposure to the potential of side effects) and the healthcare services (reduced number of visits, reduced physician and nurse time, improved outpatient management, improved cost-effectiveness).

Multiple pharmacoeconomic assessments of IIM have been performed globally. In 2011, Bhandari et al. conducted a comparative analysis of the costs of administering the newly available IV iron formulations in the UK healthcare system against the standard practice (blood transfusion and IV IS) by considering the cost of this treatment option plus nursing costs associated with administration, equipment for administration and patient transportation in the secondary care (hospital) setting across three dosage levels (600 mg, 1,000 mg, and 1,600 mg) (24). They concluded a net saving with IIM compared with iron sucrose, blood, or FCM (24). Pollock and Muduma found similar observations, also in the UK healthcare system, where the total costs were estimated to be GBP 451 per patient with IIM or LMWID, relative to GBP 594 with FCM (GBP 143 or 24% saving with IIM) or GBP 2,600 with iron sucrose (a GBP 2,149 or 83% saving) (25).

The safety and efficacy of IIM have been demonstrated across multiple therapeutic areas (26). In a recent study conducted across the USA in over 100 sites and recruiting more than 1,500 patients, IIM demonstrated statistically significant benefits in the rapid ID correction compared to IS (27). A recent analysis was performed concerning the safety of IIM using an indirect comparison with the inclusion of 8,599 patients from 21 prospective studies and compared the safety of ferric carboxymaltose (Feinject® [FCM], Vifor France SA, not currently registered in Malaysia) and IS (28). The study demonstrated that IIM reduced the odds of experiencing a serious or severe hypersensitivity reaction by 59% relative to FCM (mean odds ratio of 0.41) and by 49% relative to iron sucrose (mean odds ratio of 0.51) in a Bayesian model (24). These reductions were confirmed using a naпve pooling or random-effects meta-analysis approach (28).

Several limitations need to be taken into consideration during the decision-making process. Ideally, the target population in a budget impact analysis should include all patients who might be given the new intervention over a specified time horizon. Hence, the top-down or epidemiologic approach is usually preferred. Nevertheless, the bottom-up (market share) approach might be preferred if the submission indicates a non-inferior therapeutic conclusion. This analysis assumed equal efficacy and safety amongst all iron products (29). When the bottom-up approach was undertaken based on the actual volume use of IV iron products, only treated patients were included in the target population size. As a result, the target population size was underestimated, suggesting that the actual budget savings generated from the introduction of IIM might be more significant.

The model assumed that all IV iron products were equally effective and safe for treating ID patients. This was conditioned by assuming all patients received the same dose of iron. In practice, patients might fall out from completing the full course particularly for IS 100 mg, 10 visits were needed to achieve a targeted dose of 1,000 mg or when 3 or more hours are required to administer doses resulting in the non-availability of hospital resources or patients not willing to consent for such long treatment periods. Furthermore, Hamm et al. had observed such findings in clinical practice, especially when patients did not receive at least 3 doses of IS; the response was not different in patients who did not receive IV iron (30). Therefore, the risk of non-adherence to receiving the required dose was higher with the number of infusions needed. In turn, the efficacy of IV iron treatment might be affected.

Additional savings may be achieved due to increased patient compliance and correction of ID, including a reduction in red blood cell transfusions, improved patient outcomes post-surgical interventions, fewer re-hospitalisation episodes and a reduction in the length of hospital. This analysis has not included these potential savings to the healthcare system and can be quantified by a long-term cost-effectiveness evaluation.

CONCLUSION

The analysis in this report suggests that the uptake of IIM into the MOHM formulary listing would result in total savings of MYR 11,837,524 in the budget for IV iron products over five years from 2020 to 2024. An increasing trend in the annual budget savings due to IIM from MYR 53,910 in 2020 to MYR 5,476,782 in 2024 is forecasted. These savings are likely to be driven by the fewer visits required to achieve the targeted iron dose and the shorter IV infusion time with IIM.

ACKNOWLEDGEMENTS

The authors express appreciation to Compai Healthcare Sdn. Bhd., Jalan Damansara, 46350 Petaling Jaya, Selangor Darul Ehsan, Malaysia for the support in this study. The authors would also like to thank Jameela Sathar, haematologist of Hospital Ampang, Ong Chiew Ping, transfusion specialist of Mawar Medical Centre, Kevin Ng Wei Shan, anaesthesiologist of University of Malaya (UMMC) and Ong Kee Liang, nephrologist of Life Care Diagnostic Medical Centre as the expert advisory panel in providing input of estimations for our model.

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