

Ferric carboxymaltose: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted and actual utilisation of ferric carboxymaltose (FCM) in the first 24 months of PBS listing.

Background

FCM was listed on a cost-minimisation basis with intravenous iron polymaltose (IP) for the treatment of iron deficiency anaemia (IDA). The cost-minimisation took into account the pricing advantage for use in different treatment settings with reduced administration costs.

FCM was listed on the PBS 1 June 2014.

Data Source / methodology

The analyses used data from the Department of Human Services (DHS) supplied prescriptions database.

Key Findings

- There was a substantial growth in the total intravenous iron market after FCM was PBS-listed.
- There were 69,460 FCM prescriptions supplied in the first year of PBS listing (June 2014 to May 2015) and 125,887 prescriptions supplied in the second year (June 2015 to May 2016). In the second year, the use of FCM was higher than predicted.
- The prescriber type that wrote the largest proportion of supplied parenteral iron prescriptions was GPs.

Purpose of analysis

To compare the predicted and actual utilisation of ferric carboxymaltose (FCM) in the first 24 months of PBS listing.

Background

Iron is an essential element required for the oxygen-carrying capacity of haemoglobin in red blood cells and of myoglobin in muscle tissue. Moreover, iron plays an important role in many other vital processes in the human body. Intravenous iron preparations, such as FCM, are used for the treatment of patients with iron deficiency when oral iron preparations are ineffective or cannot be used. The aim of therapy is to replenish body iron stores and to remedy anaemia, a reduced level of haemoglobin due to iron deficiency. Before administration, a blood test is performed to calculate the dose of FCM required.¹

Iron deficiency and iron deficiency anaemia (IDA) are common conditions in Australia and can affect people of all ages and stages of life. Few studies have reported the prevalence of iron deficiency in the Australian population; however, there is a high prevalence in women and in Indigenous communities.^{2,3,4} Causes of IDA may be inadequate dietary intake of iron, malabsorption, increased iron requirements (such as in pregnancy) or as a comorbidity to an underlying condition.⁵ Untreated IDA is associated with impaired development in children, adverse effects on cognitive and physical performance in adults, and poorer maternal and infant outcomes in pregnancy.²

In most patients with IDA, first-line therapy is oral iron supplementation. Oral iron is readily available in over-the-counter products but the doses vary greatly. Parenteral iron can be used if there is an intolerance to oral iron (e.g. gastrointestinal side effects) or drug interactions, poor adherence or lack of efficacy of oral iron, malabsorption, high iron need (e.g. in haemodialysis) and where replenishment is needed rapidly.^{3,6}

The three forms of parenteral iron that are listed on the PBS are iron polymaltose (IP), iron sucrose (IS) and FCM. FCM can be rapidly infused (15 minutes or less) in single doses of up to 1,000 mg and is suitable for administration in non-hospital settings, such as by GPs and nurses in community practices. Repeat doses may be needed to meet total iron

¹ Ferinject (ferric carboxymaltose), Australian Approved Product Information. Melbourne: Vifor Pharma Pty Ltd. Approved 5 April 2011, updated 1 July 2016. Available from <https://www.tga.gov.au/product-information-pi>.

² Pasricha SRS, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olnyk JK et al. Diagnosis and management of iron deficiency anaemia: a clinical update. *Med J Aust* 2010; 193 (9): 525-532. Available at: https://www.mja.com.au/system/files/issues/193_09_011110/pas10224_fm.pdf Accessed 9 November 2016.

³ NPS MedicineWise, 1 October 2010. Available at: <http://www.nps.org.au/publications/health-professional/nps-news/2010/iron-anaemia>. Accessed 9 November 2016.

⁴ Pasricha SR. Should we screen for iron deficiency anaemia? A review of the evidence and recent recommendations. *Journal of Royal College of Pathologists of Australasia* 2012; 44 (2): 139-147.

⁵ Electronic Therapeutic Guidelines. Iron deficiency. Therapeutic Guidelines Ltd (eTG July 2016 Edition). Published March 2016. Accessed 9 November 2016.

⁶ Baird-Gunning J and Bromley J. Correcting iron deficiency. *NPS MedicineWise Australian Prescriber* 2016; 39: 193-199. DOI: 10.18773/austprescr.2016.069 Accessed 9 December 2016.

requirements.^{5,7} Refer to Dosage and administration for further details. Both IP and IS are administered intravenously, although IP can be given as an intramuscular injection using a specified technique.^{5,8} Intramuscular iron therapy is effective; however it can be painful and can result in permanent skin staining.² IP given intravenously requires an infusion time of approximately five hours; however the total iron requirement can be given in a single dose. IS has a lower risk of adverse effects than IP and small repeated doses are given to replace the total iron required.⁵

The efficacy of FCM for correcting IDA has been evaluated across a range of clinical conditions including inflammatory bowel diseases, chronic kidney disease, heart failure, heavy uterine bleeding and postpartum anaemia.⁶ Some evidence for the use of FCM in treating Restless Leg Syndrome has also been found.⁹

Therapeutic Goods Administration (TGA) approved indications

FCM is indicated for the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

Dosage and administration¹

The cumulative dose for repletion of iron using FCM is determined based on the patient's body weight and haemoglobin level and must not be exceeded. Refer to Appendix A for more details on dosage.

FCM may be administered by intravenous injection using undiluted solution up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg iron/kg body weight). For doses greater than 200 mg and up to 500 mg iron, FCM should be administered at a rate of 100 mg iron/minute. For doses greater than 500 mg and up to 1,000 mg iron, FCM should be administered over 15 minutes. More than 1,000 mg of iron should not be administered per week.

In haemodialysis-dependent chronic kidney disease patients, a single daily injection of FCM should not exceed 200 mg iron.

FCM must be administered only by the intravenous route, by bolus injection, or during a haemodialysis session undiluted directly into the venous limb of the dialyser, or by infusion. In case of infusion, FCM must be diluted only in sterile 0.9% m/V sodium chloride solution as per a dilution plan.

⁷ NPS MedicineWise Radar. Ferric carboxymaltose (Ferinject) for iron-deficiency anaemia 2014. Available at: <https://www.nps.org.au/radar/articles/ferric-carboxymaltose-ferinject-for-iron-deficiency-anaemia> Accessed 11 November 2016.

⁸ Ferrum H (iron polymaltose), Australian Approved Product Information. Melbourne: Vifor Pharma Pty Ltd. Approved 27 May 1999, updated 2 June 2015. Available from <https://www.tga.gov.au/product-information-pi>.

⁹ Wilt TJ, MacDonald R, Ouellette J, Tacklind J, Khawaja I, Rutks I et al. Treatment for Restless Legs Syndrome: Comparative effectiveness review. AHRQ Publication 2012; 86.

The current Product Information (PI) and Consumer Medicine Information (CMI) for each product are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at December 2016)

Restriction

FCM has an unrestricted PBS listing.

IP and IS have unrestricted PBS listings for prescriptions with nil repeats and an Authority Required (STREAMLINED) listing for patients with IDA undergoing chronic haemodialysis allowing up to five repeats.

Table 1: Unrestricted PBS listings of parenteral iron products

Item	Name, form & strength, pack size	Max. quantity units (mg iron) ⁶	Rpts	DPMQ	Brand name and manufacturer
10104T	Iron (as ferric carboxymaltose) 500 mg/10 mL injection, 1 x 10 mL vial ^a	2 (1000 mg)	1	\$306.96	Ferinject® (Vifor Pharma Pty Limited)
2593L	Iron (as polymaltose) 100 mg/2 mL injection, 5 x 2 mL ampoules	5 (2,500 mg)	0	\$23.16	Ferrosig® (Sigma Company Limited) Ferrum H® (Aspen Pharmacare Australia Pty Ltd)
10229J	Iron (as sucrose) 100 mg/5 mL injection, 5 x 5 mL ampoules	5 (2,500 mg)	0	\$39.53	Venofer® (Aspen Pharmacare Australia Pty Ltd)

Source: the PBS website. Special Pricing Arrangements apply.

Table 2: PBS listings of parenteral iron products with Authority Required (STREAMLINED) codes

Item	Name, form & strength, pack size	Max. quantity units (mg iron) ⁶	Rpts	DPMQ	Brand name and manufacturer
2805P	Iron (as polymaltose) 100 mg/2 mL injection, 5 x 2 mL ampoules	5 (2,500mg)	5	\$23.16	Ferrosig® (Sigma Company Limited) Ferrum H® (Aspen Pharmacare Australia Pty Ltd)
8807M	Iron (as sucrose) 100 mg/5 mL injection, 5 x 5 mL ampoules	5 (2,500mg)	5	\$39.53	Venofer® (Aspen Pharmacare Australia Pty Ltd)

Source: the PBS website. Special Pricing Arrangements apply.

For details of the current PBS listing refer to the [PBS website](#).

Date of listing on PBS

FCM was listed on the PBS 1 June 2014.

IP and IS were listed on the PBS in 1966 and 2005, respectively.

Changes to listing

At the April 2013 Special Pharmaceutical Benefits Advisory Committee (PBAC) meeting, the PBAC considered and agreed to a request to increase the number of repeats available on the listed injectable iron preparations, IP and IS, to five for patients undergoing haemodialysis. Following sponsor comment, at the July 2013 PBAC meeting, the PBAC recommended that the maximum quantity for IS's haemodialysis listing be amended back to 1.

Following a minor submission at its November 2014 meeting, the PBAC recommended amending the listing of IS to be identical to that of IP by requesting the same restriction (i.e. make the existing restriction less restrictive); and by allowing a price reduction to achieve price parity with IP. It was previously listed as an Authority Required benefit on the basis of acceptable cost effectiveness in patients who have failed prior intravenous (IV) IP therapy due to hypersensitivity reactions.

For further details refer to the Public Summary Document from the November 2014 PBAC meeting.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

At the March 2013 meeting, the PBAC recommended listing FCM on the PBS as an unrestricted benefit for IDA. Listing was recommended on a cost-minimisation basis with IV IP. The equi-effective doses were based on a 1:1 ratio of iron delivered by those formulations. The PBAC considered that there may be an advantage of FCM over IV IP in terms of reduced administration time but that this benefit had not been quantified and would need to be determined in order to justify a price advantage.

For further details refer to the Public Summary Document from the March 2013 PBAC meeting.

At the November 2013 meeting, the PBAC considered a resubmission to quantify the advantage of FCM over IV IP in terms of reduced administration time in order to justify a price advantage.

The resubmission presented a new cost analysis. The total pharmaceutical costs associated with FCM are higher than those for IP; however the resubmission claimed that patients would move to lower cost treatment settings reducing the average weighted treatment cost.

The PBAC considered that there was a clinical need for FCM in Australia as the shorter injection time was likely to provide an advantage for many groups of people who require iron treatment.

The PBAC reiterated its view that there was likely to be an advantage of FCM over IP given intravenously in terms of administration time. However the PBAC did not accept the resubmission's calculation that there would be a saving in treatment costs based on a 1,000 mg dose.

The PBAC agreed with the pre-PBAC response that the extent of any change in the setting where iron is infused is subject to a range of factors. These factors include hospital funding models, willingness and ability of general practitioners and specialists to administer IV iron in their rooms and referral practices of medical practitioners. All of these factors are likely to vary significantly between different states, territories and health care settings.

The PBAC noted that the main driver for the price difference requested was the reduction in public hospital admitted patients. The resubmission claimed that ██████% of patients were admitted as in-patients for iron infusions and ██████% were non-admitted (day only) patients. The PBAC considered that the survey data provided in the resubmission over-estimated the proportion of admitted patients and underestimated the non-admitted patients. In addition, the PBAC considered that the proposed changes in private hospitals were unlikely to occur owing to the business models in place.

The PBAC noted that when the proportions of IP use in public hospitals as inpatients and outpatients were reversed from that proposed in the resubmission, the proportion of FCM use in private hospital inpatients was higher than that proposed in the resubmission. Further, the proportion of private hospital outpatient use was the same for both IP and FCM and the proportions of use in general practice remained the same. With these changes, the difference in treatment costs resulted in a higher weighted treatment cost than that calculated in the resubmission. The PBAC noted that on the basis of this revised calculation, a price reduction would be required.

The PBAC considered that the resubmission's approach to preparing the estimates was reasonable. The PBAC agreed with DUSC that the treatment survey used had a number of internal and external validity issues and considered that the extent of switching to community based GP settings could be inflated in the survey.

The PBAC also noted the ESC and DUSC concerns regarding the possible use in haemodialysis patients where there is no administrative cost advantage, and that there was potential for the 500 mg vial to be used for lower doses.

The PBAC noted that the sponsor reduced the cost of the 500 mg vial to address the potential use of doses greater than 1,000 mg; however, the PBAC noted that the pre-PBAC response did not address the potential use in patients requiring smaller doses than 500 mg. Therefore the PBAC considered that the dispensed price for maximum quantity (DMPQ)

proposed in the pre-PBAC response was poorly justified and that the expected price advantage for FCM compared to IP would be lower.

On the basis of the costing model in the submission, the PBAC requested the Department calculate a cost-minimised price using the revised treatment setting proportions. The PBAC recommended that the price should take account of the variability in proportions of inpatient and outpatient administration as well as the variability in administration of iron in GP settings.

The PBAC considered that the Department should negotiate a risk sharing arrangement with the sponsor to mitigate the risk of wastage and the potential for larger market uptake in patients treated in health settings with little or no administration benefit. The PBAC did not consider an Authority Required listing would be justified for the purposes of a risk sharing arrangement.

For further details refer to the Public Summary Document from the November 2013 PBAC meeting.

Approach taken to estimate utilisation

DUSC reviewed the resubmission of FCM for IDA. The submission used a scenario-based market share approach, with and without FCM available. The base case estimates assumed a standard dose of 1,000 mg of iron. DUSC considered the extent of use and financial estimates presented in the submission to be underestimated. DUSC considered that the estimated number of patients treated with FCM was sensitive to the market size at baseline, market growth and FCM uptake. The financial impact was also sensitive to the dose prescribed and redistribution across treatment settings. Refer to Appendix B for financial estimates.

From a quality use of medicines perspective, DUSC considered that due to its convenience over IP, FCM may have an important role in reducing unnecessary use of red cell transfusion, and for replenishment of iron stores in patients who require transfusion to avoid further IDA episodes. It should be noted that PBS-subsidised FCM is not able to be prescribed to hospital inpatients, and so the availability of FCM in individual hospital formularies will impact uptake.

The PBAC agreed with DUSC that FCM may facilitate greater use of iron infusions in specific settings where IDA was a significant health issue and access to hospital-based care was extremely limited, in particular remote and regional areas. However, they also considered that the uptake and delivery of services by GPs would be highly variable across Australia and dependent on various factors such as activity-based funding and resource utilisation in hospitals, fees for MBS services, and availability of equipment for infusion and monitoring.

The PBAC considered that the resubmission's approach to preparing the estimates was reasonable. The PBAC agreed with DUSC that the treatment survey should be interpreted with caution due to external and internal validity concerns. In particular the PBAC agreed that the distribution of patients in non-admitted and admitted settings reported in the survey was highly variable and considered that the estimated proportions of people switching iron administration from hospital inpatient to hospital outpatient settings was inflated. The PBAC noted DUSC's advice that more clinics, employing nurses to deliver services such as FCM administration, may be set up in community settings in the future.

The final agreed estimates differed from the estimates in the resubmission, as they incorporated the DUSC advice 'that the number of GP consultations where IP is currently prescribed could potentially be three times higher than presented in the resubmission'.

Table 4: Resubmission and (final agreed estimates) for cost analysis

Row	Parameter	Value	Source	Comments
A	Total admitted separations	██████	AIHW 2009-10	Includes ██████ same-day admitted patients and ██████ non-same-day admitted patients (AIHW break-down)
B	Proportion admitted	████	Treatment survey	The treatment survey results provides the best estimate on the proportion admitted - noting the admitted separation includes same-day and non-same-day admissions
C	Non-admitted presentations	██████	(A*1/B)-A	N/A
D	Proportion public	██████	NHCDC 2008-09	
E	Proportion private	██████	1-D	
F	Number admitted public	██████	A*D	
G	Number admitted private	██████	A*E	
H	Number non-admitted public	██████	C*D	
I	Number non-admitted private	██████	C*E	
J	Number GP	██████	GPRN 2012-2013	Increase in Number of GP to reflect all IDA patients and correlates to DUSC advice
K	Total episodes	██████	Sum(F:J)	N/A
L	Proportion admitted public	██████	F/K	Changed due to change in number of GP episodes
M	Proportion admitted private	██████	G/K	
N	Proportion non-admitted public	██████	H/K	
O	Proportion non-admitted private	██████	I/K	
P	Proportion GP	██████	J/K	

The PBAC also noted DUSC’s concerns regarding the possible use of FCM in haemodialysis patients, where there is no administrative cost advantage and that there was potential for the 500 mg vial to be used for lower doses.

For further details refer to the Public Summary Document from the November 2013 PBAC meeting.

Methods

The analyses used data from the DUSC database and the Department of Human Services (DHS) supplied prescriptions database.

The DHS supplied prescriptions database includes data submitted to DHS for payment of a PBS/RPBS subsidy by the Government. This database includes actual under co-payment

prescription data from 1 April 2012. Patient counts were based on de-identified unique patient identification numbers (PINs) from the prescription data. This allows patients to be classified as new patients and to identify prior treatments. The DHS database was used for patient level analyses; including initiating and prevalent, prescriber type, location and setting analyses.

Patients initiating therapy (or 'new patients') were defined as those who were supplied their first parenteral iron prescription in that month and year, with a 12 month look-back. A sensitivity analysis was also conducted using a 24 month look-back. For the treatment of iron deficiency, it is likely that patients may require a single supply of iron. If additional supplies are required, it may not be within the same year. Therefore, if a patient is supplied an additional prescription of iron 12 or 24 months after the very first supply, it can be deemed a new episode of treatment.

For the utilisation of FCM per patient analysis, a cohort of patients who initiated FCM between 1 December 2014 and 31 May 2015 were followed over a 12 month period since their initial supply. The number of packs of FCM that they each were supplied over their individual 12 month follow-up was counted.

To analyse the use of FCM in rural and remote areas, prescriptions are displayed by Statistical Area Level 3 (SA3) area. The number of prescriptions in Year 2 of PBS listing (June 2015 to May 2016) were converted to SA3 using the ABS Postcode 2011 to Statistical Area Level 3 2011 correspondence. The number of prescriptions per SA3 were standardised by 100,000 population using the 2015 Estimated Residential Population from ABS.Stat.

There are special PBS supply arrangements for clients of eligible remote area Aboriginal Health Services (AHS). AHS are able to receive bulk supplies of PBS medicines through an approved community or hospital pharmacy. Data on items supplied to AHS include the item and quantity supplied, month of supply, the name of the AHS, state and cost to Government. The supply data relate to the pharmacy supplying the items to the AHS. For medicines supplied to AHS, there are no data on whether the products were supplied to patients or any other patient-level data.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available DHS Medicare date of processing data.¹⁰ The publicly available DHS Medicare data only includes subsidised PBS/RPBS prescriptions with prescriptions under the patient co-payment not included. The DHS Medicare data used in this report includes under co-payment prescriptions from 1 April 2012.

¹⁰ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Analysis of drug utilisation

Figure 1 shows the total number of parenteral iron prescriptions over time, including the number of FCM, IP and IS prescriptions.

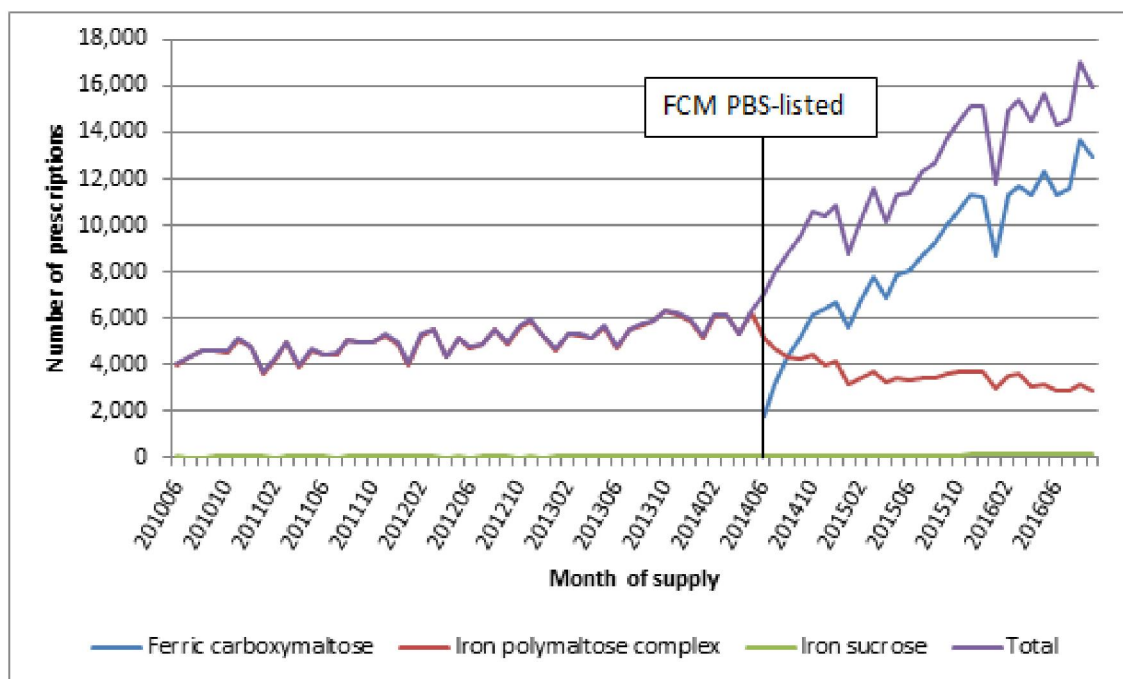


Figure 1: Number of PBS parenteral iron prescriptions supplied by month

Prescriptions by date of supply. FCM PBS-listed 1 June 2014. Source: DHS database accessed December 2016.

The use of parenteral iron had been increasing gradually until June 2014. Uptake of FCM has been high and rapid, and has grown the parenteral iron market substantially. Use of IP declined following the listing of FCM and has stabilised at a lower level. IS use has remained low.

The estimated use of FCM was presented in the submission as ‘episodes’ of a standard dose of 1,000 mg iron. If a patient requires a dose of iron greater than 1,000 mg for an episode, an additional prescription (or repeat) would be required for FCM whereas the maximum quantity of IP provides a sufficient quantity for either a higher dose in the infusion or a repeat infusion (see Table 1). Therefore ‘episodes’ and prescriptions may not be comparable. To assess the extent of any difference, the proportion of FCM prescriptions with a repeat was determined. An analysis of the PBS data (not shown) found that 70% of original prescriptions dispensed were ordered with nil repeats, and that 93% of all FCM prescriptions dispensed were original prescriptions. This indicates that the majority of episodes are likely to be for a standard dose of 1,000 mg.

The frequency of use will vary across a range of patients and conditions. Table 5 shows the number of 500 mg vials of FCM supplied to patients over a 12 month period.

Table 5: Number of FCM vials supplied to a cohort* of patients who received an initial supply of FCM

Total number of vials over 12 months	Number of patients (% of total)
1	1,829 (5.44%)
2	24,574 (73.04%)
3	582 (1.73%)
4	5,028 (14.94%)
5	114 (0.34%)
6	955 (2.84%)
7-10	462 (1.37%)
11-14	75 (0.22%)
15-18	17 (0.05%)
≤19	9 (0.03%)

Source: DHS database accessed November 2016.

*Cohort includes all patients initiating FCM between 1 December 2014 and 31 May 2015, followed over a 12 month period since their initial supply.

The majority of patients in this cohort were supplied one prescription (two vials with a total of 1,000 mg of iron) over the 12 months. The second largest proportion of patients was supplied two prescriptions (2,000 mg). A small number of patients received a large number of vials. This may indicate some use of FCM for haemodialysis patients.

Table 6 shows the number of treated and new patients who were supplied parenteral iron in the two years before and after FCM was PBS-listed, with associated annual growth.

Table 6: Number of parenteral iron patients in each year before and after FCM was PBS-listed

Year	Treated patients (% growth)	New patients (% growth)
June 2012 to May 2013	39,408 (N/A)	33,131 (N/A)
June 2013 to May 2014	44,278 (12.4%)	37,646 (13.6%)
June 2014 to May 2015 ¹	87,433 (97.5%)	79,524 (111.2%)
June 2015 to May 2016	129,225 (47.8%)	115,423 (45.1%)

¹ FCM PBS-listed 1 June 2014.

Parenteral iron includes FCM, IP and IS. Source: DHS database accessed December 2016.

There was 13.6% growth in new patients in the year before FCM listing compared to 111.2% growth in the year that it was listed. The subsequent year had 45.1% growth in new patients.

Analysis by prescriber type

Figure 2 shows the number of parenteral iron prescriptions (FCM, IP and IS) by prescriber type and year.

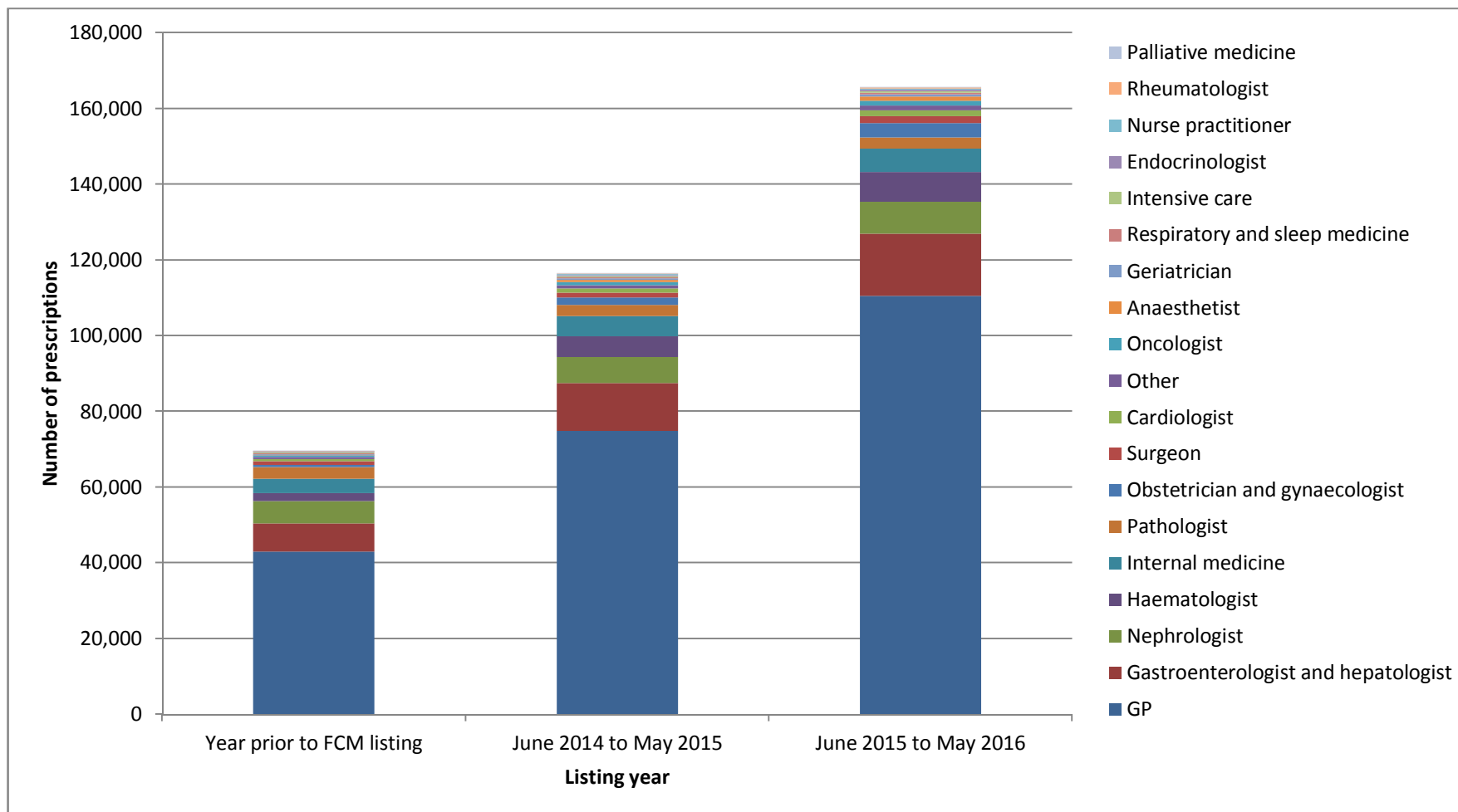


Figure 2: Number of parenteral iron prescriptions by prescriber type and year

FCM PBS-listed 1 June 2014. Source: DHS database accessed November 2016.

There were many different types of prescribers who provided prescriptions for parenteral iron. The largest proportion of prescriptions supplied was written by GPs. Gastroenterologists and hepatologists, nephrologists and haematologists were the next most common prescribers. The highest rate of growth has been for prescriptions prescribed by nurse practitioners, anaesthetists and palliative medicine specialists, but their contribution to the total number of prescriptions was very small.

Analysis by setting

A key uncertainty when predicting the costs and use of FCM was the distribution of patients across treatment settings. Figure 3 depicts the number of prescriptions for parenteral iron (FCM, IP and IS) by listing year and dispensing setting. The results need to be interpreted in the context that medicines used for public hospital inpatients are not subsidised through the PBS (and therefore not visible in this data), and that community pharmacies may provide services to private hospitals and outpatient clinics.

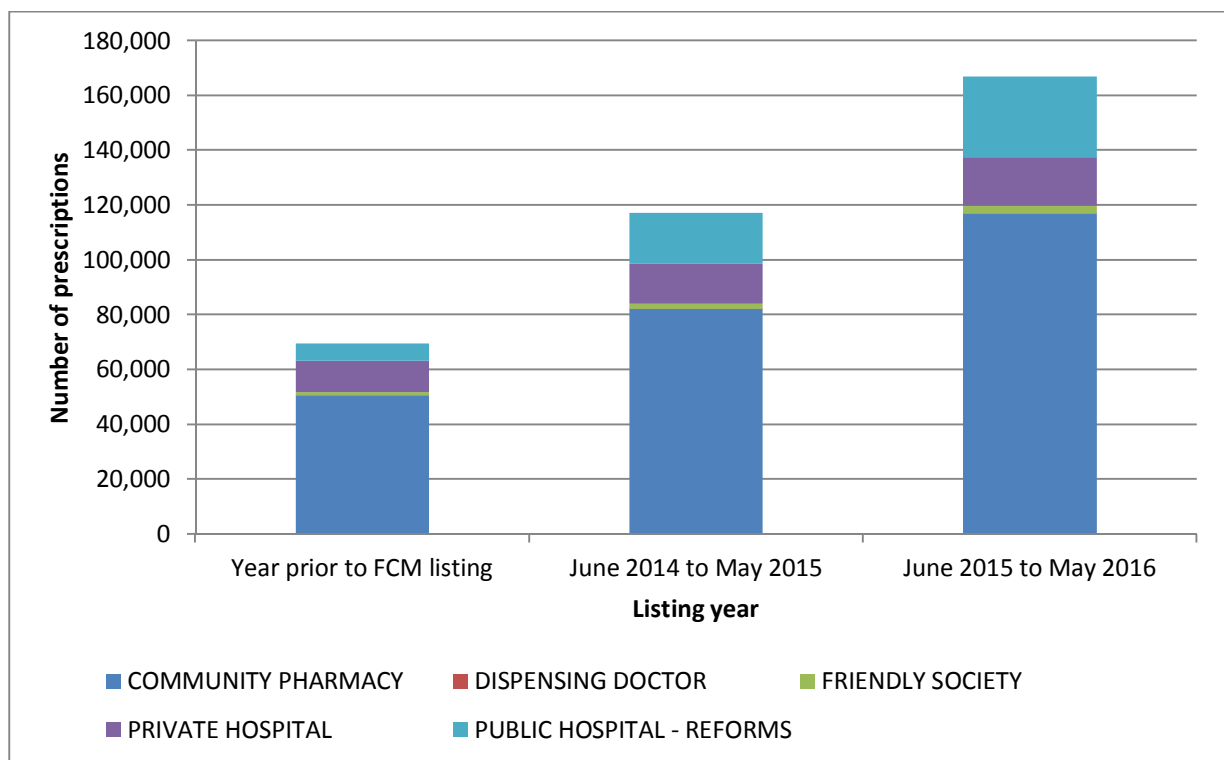


Figure 3: Number of total parenteral iron prescriptions by setting and listing year

FCM PBS-listed 1 June 2014. Source: DHS database accessed November 2016.

In the year before FCM was listed and in the two years afterwards, the highest number of prescriptions was supplied by community pharmacies.

While community use represents the greatest increase in the volume of prescriptions dispensed, the highest rate of growth has been in public hospitals participating in PBS reforms. These hospitals can supply PBS medicines for outpatient and day-admitted patients. The number of parenteral iron PBS prescriptions supplied by public hospitals tripled in the first year that FCM was available compared with the previous year (from

6,456 to 18,324 prescriptions) This may indicate some shift from inpatient to outpatient/day admitted setting. However, this cannot be verified from PBS data.

A breakdown of the prescriptions dispensed by setting for each medicine is provided in Appendix C.

Analysis by region

The PBAC and DUSC considered that FCM may facilitate greater use of iron infusions in specific settings where IDA was a significant health issue and access to hospital-based care was extremely limited, in particular remote and regional areas. The uptake and delivery of services would be highly variable across Australia and dependent on numerous factors. Figure 4 depicts the number of FCM vials supplied by region.

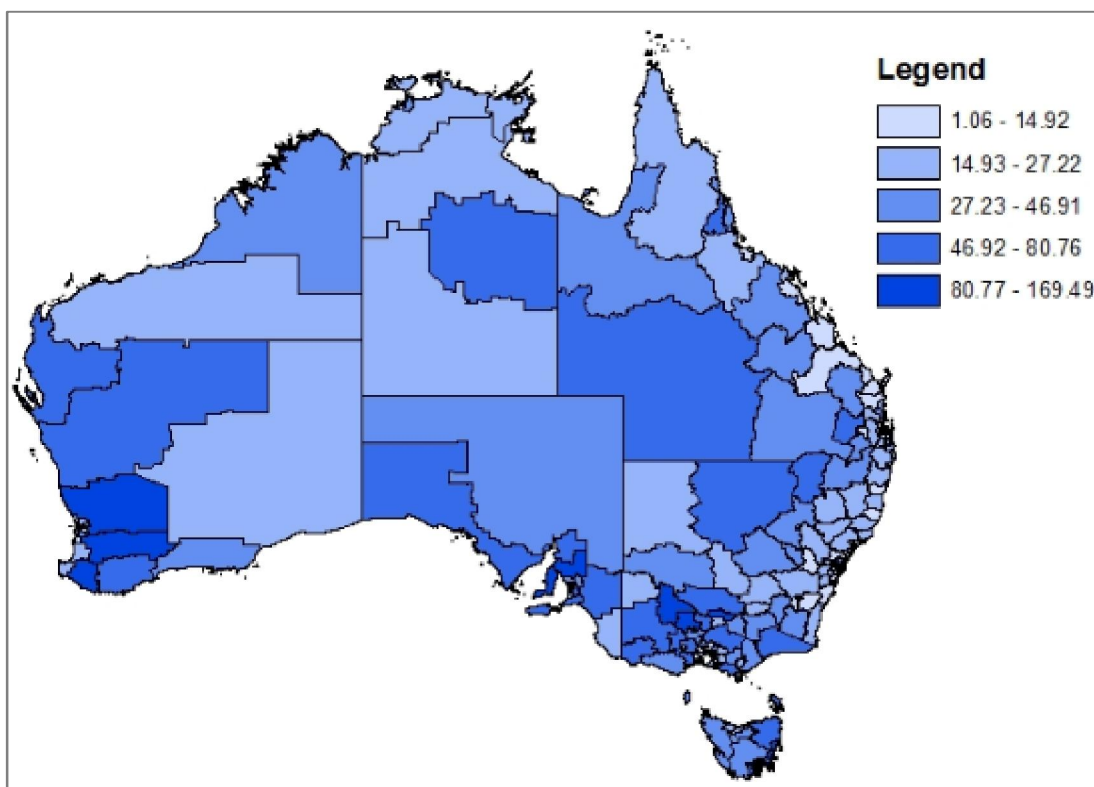


Figure 4: Number of FCM prescriptions in the second year of listing (June 2015 to May 2016) by SA3, standardised by 100,000 population

There was variability of use across Australia. A number of the more densely populated areas, such as those along the east coast, had lower rates of prescriptions supplied compared to the more regional areas further inland.

Pack data from Aboriginal Health Services (AHS)

The prevalence of IDA is high among Aboriginal populations. AHS are able to receive bulk supplies of PBS medicines through an approved community or hospital pharmacy. The total number of vials of FCM supplied through the AHS in the first year of listing was 728. In the second year it was 1,273.

Analysis of expenditure

Table 7 shows the government expenditure for FCM, IP and IS in the first two years of listing of FCM.

Table 7: PBS benefits for parenteral iron

Listing year	FCM	IP	IS	Total market
Year 1 (June 2014 to May 2015)	\$19,292,165	\$982,946	\$58,953	\$20,334,064
Year 2 (June 2015 to May 2016)	\$34,505,573	\$632,542	\$22,748	\$35,160,863

Special pricing arrangements apply for FCM. Source: DHS database using date of supply, which may be slightly different to publicly available Medicare Australia date of processing data, accessed November 2016.

Analysis of actual versus predicted utilisation

This analysis compares the estimates of utilisation agreed between the Sponsor and the Department prior to listing. IS has not been included as the numbers are negligible. The actual numbers reflect all PBS prescriptions for FCM and IP.

Table 8: Predicted versus actual numbers of FCM and IP prescriptions (patient episodes of 1,000 mg)

	Year 1 ^a			Year 2 ^b		
	FCM	IP	Total market (FCM as % of total market)	FCM	IP	Total market (FCM as % of total market)
Predicted	██████	██████	██████	██████	██████	██████
Actual	69,460	48,727	118,187 (59%)	125,887	41,763	167,650 (75%)
% Difference (A-P)/P	██████	██████	██████	██████	██████	██████

^a Year 1: June 2014 to May 2015

^b Year 2: June 2015 to May 2016

Source: Patient data from DHS supplied prescription database accessed November 2016.

It was predicted that there would be a shift in the total market from IP to FCM. Whilst in year 1 the number of actual prescriptions for FCM was similar to predicted, there was not the anticipated drop in IP prescriptions. The total market was ██████% higher than predicted. In year 2, the number of prescriptions for FCM was ██████% higher than predicted with the total market being over ██████% higher than expected.

Discussion

Since the listing of FCM on the PBS, the parenteral iron market has grown substantially (Figure 1). The actual use of FCM has been higher than predicted for a number of reasons:

Baseline parenteral iron market

It is very likely that the baseline market for parenteral iron was underestimated. Two sources were used to estimate the baseline market – GPRN data to estimate use of parenteral iron in the GP setting, and hospital separations with a principle diagnosis of IDA.

The GPRN data gave a national estimate of [REDACTED] GP consultations resulting in a prescription for IP, but only the [REDACTED] episodes where the exact reason for prescription recorded was 'iron deficiency anaemia' were included in the submission estimates. DUSC considered that the number of GP consultations where IP is prescribed could potentially be three times higher than presented in the resubmission, resulting in an underestimate of the baseline market and representing closer to 50% of the distribution across treatment settings. The final estimates agreed between the Sponsor and the Department used a midpoint of [REDACTED] episodes in the GP setting.

[REDACTED]

Market growth

The baseline market growth was derived from the average annual growth in PBS prescriptions processed for IP from 2008 to 2012 (8.8%). The submission assumed that there would be additional growth in the total parenteral iron market with availability of FCM (an additional [REDACTED]% and [REDACTED]% growth in year 1 and year 2 of listing, respectively). DUSC had agreed that IDA was likely to be undertreated due to perceived and actual problems with use of oral and available subsidised parenteral iron. While DUSC considered the assumption of additional market growth to be reasonable, it was noted that the extent of current underutilisation had not been quantified in the resubmission.

Additional market growth has greatly exceeded expectations. The total number of parenteral iron prescriptions in the first year that FCM was available on the PBS (118,187) was [REDACTED]% higher than expected ([REDACTED]), but noting that some of this difference is due to an underestimation of the baseline market. In the second year the parenteral iron market was more than [REDACTED]% above that expected. One reason may have been a higher than anticipated unmet clinical need in the market for an alternative iron infusion. However, there may also be use of FCM in a broader population of patients such as for iron deficiency without anaemia, or in patients with symptoms (e.g. fatigue) but without confirmed IDA.

Parenteral iron market share

The submission had assumed a market share for FCM of [REDACTED]% in year 1 increasing to [REDACTED]% in year 5 of listing. DUSC had considered it likely that uptake of FCM in place of intramuscularly administered IP would be high and rapid due to actual and perceived problems with IP (pain, skin stains, risk of anaphylaxis). The GPRN data showed that FCM already had at least [REDACTED]% of the market before PBS listing. The uptake of FCM in the final agreed estimates was [REDACTED]% in year 1 increasing to [REDACTED]% by year 5.

The market share of FCM was 59% in year 1 increasing to 75% in year 2. Although the total use of FCM was much higher than predicted, the market share was lower because FCM has added to the market rather than substituting IP to any great extent (Figure 1).

Dose

The resubmission reasoned that IV iron is typically administered as a standard dose of 1,000 mg, irrespective of the degree of deficiency present. This was based on a 'standard dose of IV iron' question from a treatment survey of [REDACTED]

[REDACTED]. In November 2013, the PBAC agreed with DUSC that the survey should be interpreted with caution due to external and internal validity concerns.¹¹ The survey used to determine the standard dose included haemodialysis patients. The November 2013 pre-PBAC response acknowledged that some patients with more severe IDA will require a higher dose in routine clinical practice and proposed a price reduction of [REDACTED]% so that FCM would deliver cost savings in terms of total treatment costs and be at least cost neutral in the highest dose of 2,000 mg.

Whilst the most common number of vials per patient over a 12 month period was two (equalling 1,000 mg; see Table 5), about 16.7% of patients required three or four vials (1,500-2,000 mg). A smaller proportion (5.4%) required only one vial. Given the higher price of FCM and the requirement for multiple prescriptions to achieve doses above 1,000 mg compared with IP, it is possible that cost-neutrality has not been realised. It is recognised that an analysis over the 12 month period may include more than one 'episode' of treatment. DUSC may wish to advise whether alternative analyses or sources of data, such as MedicineInsight, would be helpful to assess the range of doses used in practice. The amount of wastage could potentially also be ascertained if the prescribed dose has been recorded by the GP.

A small number of patients receive large quantities of iron. There are circumstances where regular doses of iron are required for IDA. Figure 2 shows that there are a wide range of practitioners who prescribe IV iron, indicating its use across a number of specialities. At the time of the resubmission, there were concerns regarding the possible use of FCM in haemodialysis patients, where there is no administrative cost advantage and that there was potential for the 500 mg vial to be used for lower doses. [REDACTED]

¹¹ The Pharmaceutical Benefits Advisory Committee Public Summary Document for ferric carboxymaltose November 2013. Available at <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-11/ferric-carboxymaltose>

Distribution across treatment settings

The total pharmaceutical costs associated with FCM are higher than those for IP; however the resubmission predicted that patients would move to lower cost treatment settings reducing the average weighted treatment cost.

The Sponsor (Pre-PBAC response November 2013 p2) noted that shifts across settings depend on a wide range of factors, such as prevailing hospital funding models, the willingness and ability of individual general practitioners and specialists to administer IV iron by slow push injection and the referral practices among IDA patients. Each of these is likely to vary significantly within and between different States, Territories and healthcare settings. The PBAC agreed, and considered that the uptake and delivery of services would be different across Australia and dependent on factors such as activity-based funding and resource utilisation in hospitals, fees for MBS services, and availability of equipment for infusion and monitoring.

Data is not available to assess use across all settings hence the necessity for the treatment survey (despite limitations) in the resubmission. More recent hospital separations data are not yet available to assess whether the anticipated reduction in public hospital inpatient admissions, and consequential increase in non-admitted patients, has been realised. The highest rate of growth has been in public hospitals participating in PBS reforms. The number of parenteral iron PBS prescriptions supplied by public hospitals tripled from year one to year two, which may indicate some shift from inpatient to an outpatient or day admitted setting (Figure 3). However, this cannot be verified from PBS data. Given the magnitude of the increase in the total parenteral market it seems likely that the use across all settings has grown, rather than there being substantial shift between settings. The greatest absolute increase in parenteral iron is for FCM prescribed by GPs.

DUSC had noted that uptake in rural and remote settings had not been separately quantified in the resubmission, but considered it may be higher than in the general population. Figure 4 illustrates that the use of FCM has been variable across Australia. There appears to be greater quantities supplied in more regional areas than in higher density areas.

The 75% increase in supply of FCM via the Aboriginal Health Services from the first year to the second may indicate that uptake is increasing for a population that has a high prevalence of IDA.

Overall the actual use of FCM has been higher than predicted due to an underestimate in the size of the baseline market and the unmet clinical need for a new IV iron infusion; the potential use in dialysis patients; and the use in a broader population.

DUSC consideration

Overall DUSC considered that the use of FCM has been higher than predicted due to a range of factors including:

- an underestimate of the size of the baseline treated and untreated IDA populations.

- a likely shift from the oral market for patients inadequately treated with oral iron due to dose-related gastrointestinal effects or for those people where FCM is preferred due to ease of administration or other factors.
- higher than expected uptake, which may be influenced a result of increased general awareness of IDA and education around the detection and management of IDA.

Market growth

DUSC discussed the potential reasons for the large growth in the market. A key driver is likely to be uptake in the untreated IDA population, which was not quantified in the submission, but accounted for the market growth assumption to some extent. DUSC also considered that some of the growth may be due to a shift from the oral iron market. A wide range of oral iron formulations are available over the counter and are relatively inexpensive. This shift may be from patients inadequately treated with oral iron due to dose-related gastrointestinal effects, but also from people who prefer FCM due to ease of administration or other factors. DUSC noted that this latter group was not the population expected to use FCM and were not included in the economic model or financial estimates. DUSC also considered that, despite difficulty in determining the length of an episode of treatment, the report (Table 6) indicates that much of the market growth can be attributed to new parenteral iron patients. The sponsor (in the pre-DUSC response) provided an analysis of IMS data demonstrating that the Australian oral iron market was relatively flat through 2008-10, but began to increase following the release of new local guidelines in 2010-11; and both the overall market and rate of growth have continued to increase since the PBS listing of FCM in June 2014. DUSC noted that the use of oral iron prior to FCM cannot be ascertained from available data.

DUSC noted increased education for health professionals and awareness of appropriate use of blood products and management of IDA may also influence rates of prescribing of iron. In the pre-DUSC response, the sponsor noted that NPS MedicineWise and the National Blood Authority of Australia updated their guidelines for the management of IDA and the use of iron products. Various Commonwealth and State/Territory government initiatives also drove uptake of these guidelines. In addition, the National Heart Foundation's guidelines on heart failure management were updated in 2011 and incorporated the need to identify and treat iron deficiency.

Parenteral iron market share

DUSC noted there has been no substantial shift to FCM from the IP market, as FCM has added to the market rather than substituting IP to any great extent. In the pre-DUSC response, the sponsor considered that PBS use of IP stabilising at a lower level likely represents the prevalent haemodialysis population.

Dose

A small number of patients received large quantities of iron. There are circumstances where regular doses of iron are required for IDA. DUSC noted that the majority of people received one prescription of two vials (1,000 mg).

Figure 2 shows that there are a wide range of practitioners who prescribe IV iron, indicating its use across a number of specialities. DUSC noted the large array of prescribers who are supplying FCM to patients.

Distribution across treatment settings

DUSC noted that the proportion of parenteral iron prescribing by GPs has not changed greatly (62% in year before FCM was listed increasing to 66% in second year of listing).

DUSC noted that savings across the overall healthcare setting cannot be determined due to data limitations. Since FCM has been available on the PBS for 24 months, prescribers and nurses are now more familiar with FCM and its administration, which may further increase its use in community settings.

DUSC noted that uptake of FCM has been variable across Australia (Figure 4). DUSC noted that the increased use in various regions of Australia may reflect educational activities undertaken in those areas and infusion programs/clinics that are underway. It was also promising to see increased use by the Aboriginal Health Services and in areas they are located in.

DUSC actions

DUSC requested that the report, stakeholder response and DUSC minutes be provided to the PBAC.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor comments

Vifor strongly believes that the majority of use of FCM in the PBS setting has been clinically appropriate and cost effective and that the major reasons for any observed differences between estimated and actual real world use are related to naïve underestimation of the baseline patient population and the extent of true clinical need, rather than use beyond the intended treatment setting.

There is no evidence currently available indicating that FCM is being used to any significant extent within inappropriate patient populations (haemodialysis or mild to moderate iron deficiency) or at inefficient dose levels (<500 mg or > 1,000 mg). Moreover, while evidence regarding an anticipated shift in patients away from hospital inpatient settings is pending, prescribing patterns for FCM certainly indicate that it is being used primarily in a GP & community setting, as predicted and intended.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix A: Dosage of FCM

There are two methods for determining the cumulative dose, the Ganzoni Method and the Simplified Method. Caution is recommended with the Simplified Method since it is based on experience in a single trial in adults with median haemoglobin (Hb) 104 g/L (range 61-146 g/L) and body weight ≥ 35 kg. Patients should be closely monitored when large single doses of FCM (>200 mg iron) are administered since the safety data are limited.

Post repletion, regular assessments should be done to ensure that iron levels are corrected and maintained.

Ganzoni Method

Cumulative iron dose = body weight in kg x (target Hb – actual Hb g/L) x 0.24 + iron stores in mg. Where:

- target Hb = 130 g/L for body weight and
- iron stores = 15 mg/kg body weight for body weight. Round down to nearest 100 mg if body weight ≤ 66 kg and round up to nearest 100 mg if body weight >66 kg.

Simplified Method (for patients of body weight ≥ 35 kg)

Table 9: The cumulative iron dose using the Simplified Method

Hb g/L	Body weight 35 to < 70 kg	Body weight ≥ 70 kg
<100	1,500 mg	2,000 mg
≥ 100	1,000 mg	1,500 mg

Appendix B: Base case financial estimates from November 2013 resubmission (final agreed estimates in brackets)

		Year 1	Year 2	Year 3	Year 4	Year 5	Sources/Assumptions
Estimated extent of use							
1	Total patient episodes 1,000 mg iron without FCM listing	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Baseline [REDACTED] episodes sum of : - 31,790 hospital separations with principle diagnosis IDA - [REDACTED] additional ([REDACTED]%) not formally admitted (clinician survey) - [REDACTED] GP episodes (GPRN database) - 9% growth (Medicare IP data)
2	Total patient episodes 1000 mg iron with FCM listing	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Baseline [REDACTED] episodes as above and additional market growth assumption of [REDACTED]% Y1, [REDACTED]% Y2 & 3, and [REDACTED]% Y4 & Y5 as access to FCM overcomes previous 'blockages in clinical access to IV iron'
3	FCM market share	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Submission assumption
4	FCM patient episodes	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Row 2 * Row 3
Estimated cost to the PBS for FCM							
5	Total cost of FCM (DPMQ)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Row 4 * DPMQ 1,000 mg FCM (\$ [REDACTED]) [REDACTED]
6	Net cost minus co-payment	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Patient co-payment based on 2012 IP Medicare data [REDACTED]
Estimated changes in use and cost of other drugs							
7	Difference in episodes of IP without & with FCM	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Row 2* (1-Row 3) – Row 1

8	Net decrease IP costs minus co-payment	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Row 7 *(DPMQ 1000 mg IP (\$68.02) – average co-payment (\$17.69)) Patient co-payment based on Medicare data for IP in 2012
Net financial impact of listing on the PBS/RPBS							
9	Net cost to PBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Row 6-Row 8 [REDACTED]

Source: DUSC advice October 2013 p4. Final agreed estimates in brackets. [REDACTED].

FCM: ferric carboxymaltose, IDA: iron deficiency anaemia, IP: iron polymaltose

Appendix C: Number of prescriptions for FCM, IP and IS by setting

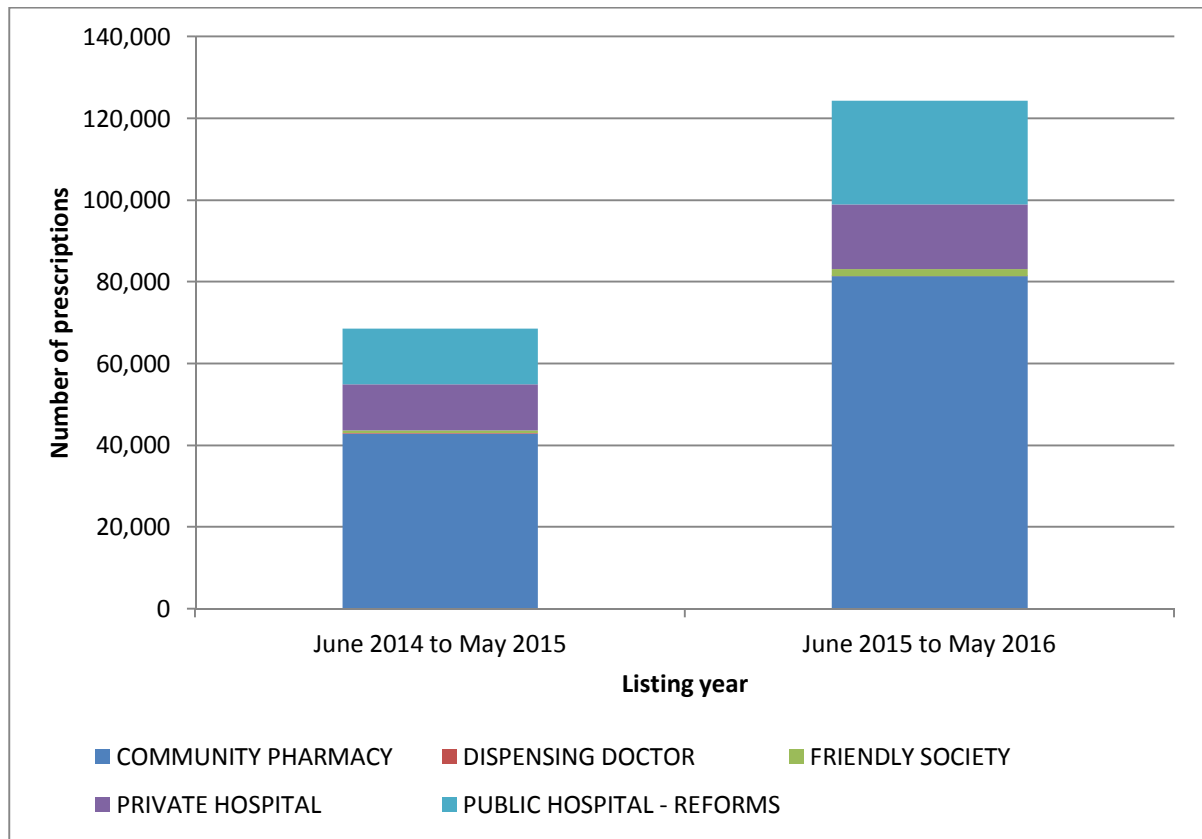


Figure 5: Number of FCM prescriptions by setting and listing year

FCM PBS-listed 1 June 2014. Source: DHS database accessed November 2016.

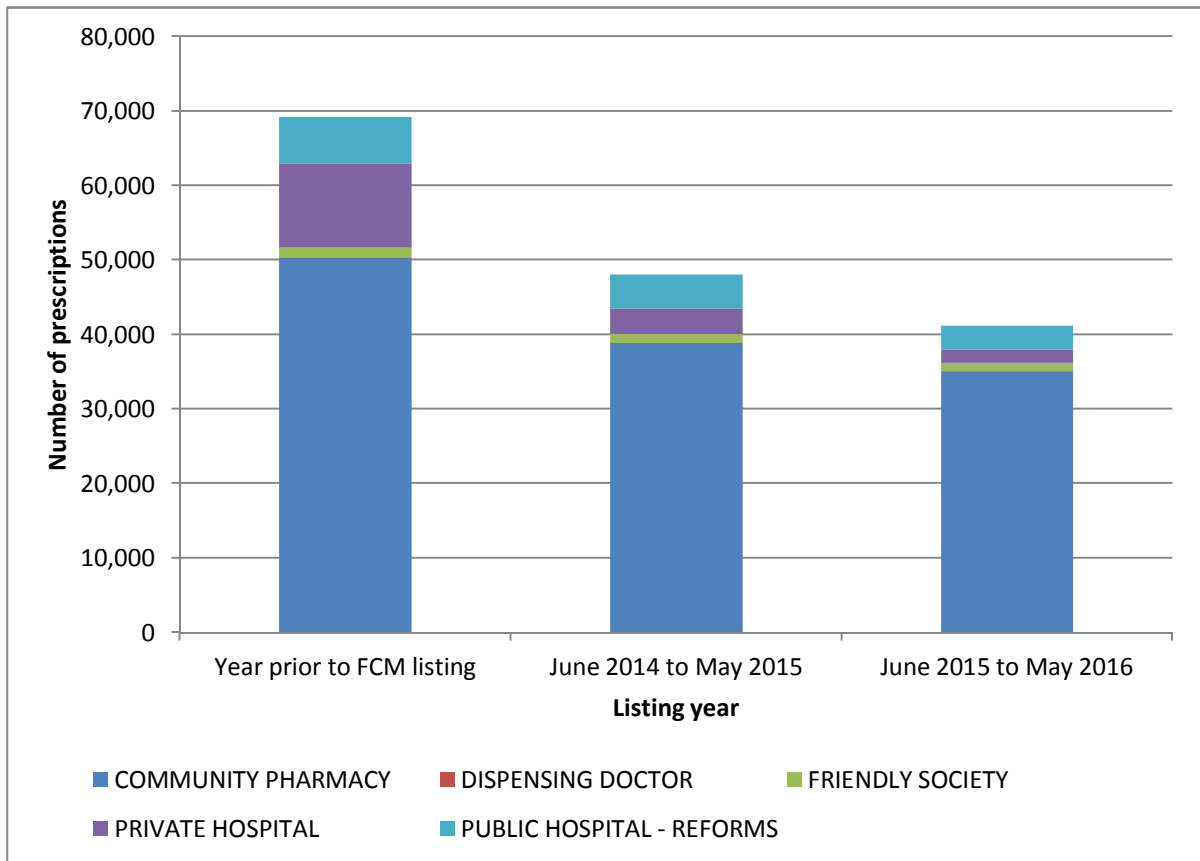


Figure 6: Number of IP prescriptions by setting and listing year

FCM PBS-listed 1 June 2014. Source: DHS database accessed November 2016.

The number of prescriptions dispensed by private hospitals has decreased in the two years after FCM was listed.

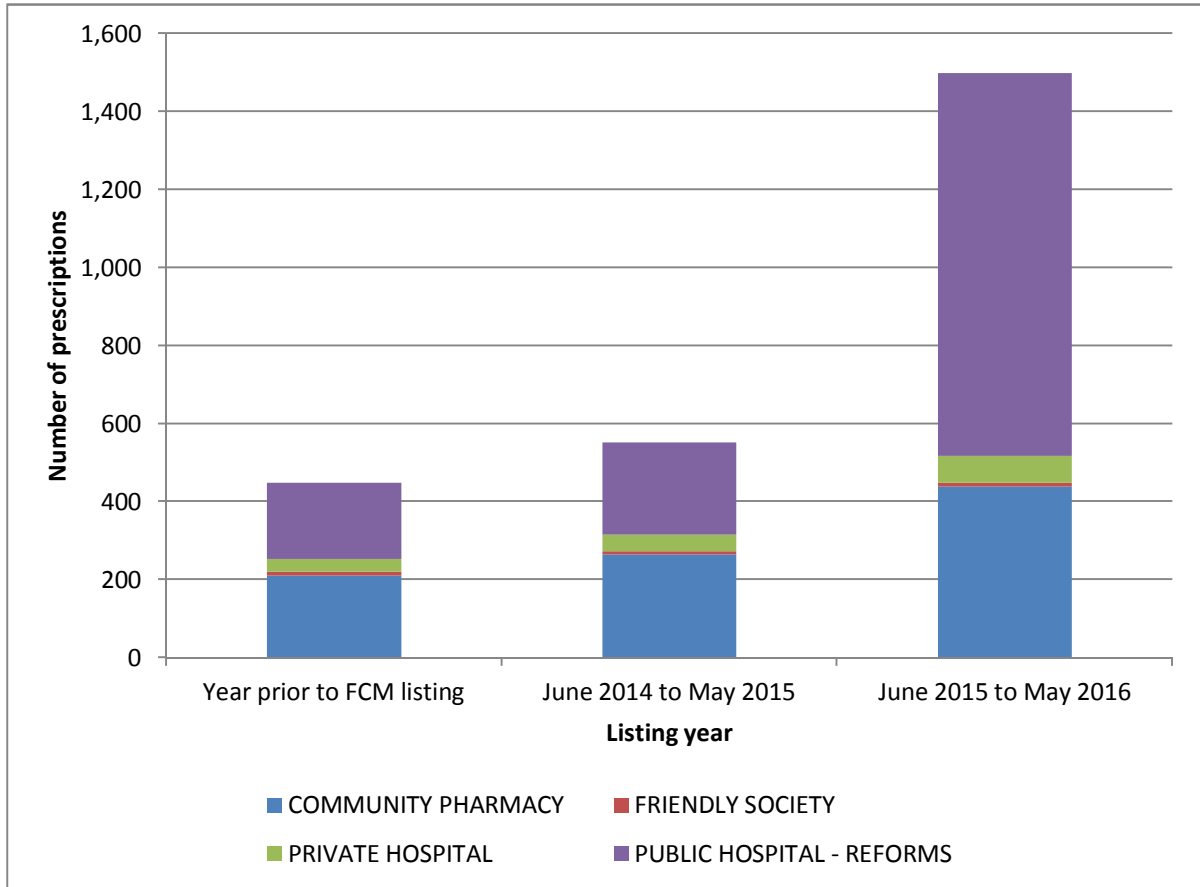


Figure 7: Number of IS prescriptions by setting and listing year
 FCM PBS-listed 1 June 2014. Source: DHS database accessed November 2016.