PUBLIC SUMMARY DOCUMENT
Product: Ferric Carboxymaltose, solution for injection, 100 mg in 2 mL and 500 mg in 10mL, Ferinject®
Sponsor: ViforPharma Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application
The submission requested an Authority Required listing for the treatment of iron deficiency anaemia (IDA), where oral iron preparations are not tolerated, ineffective or otherwise inappropriate.

2. Background
The product had not been previously considered by PBAC.

3. Registration Status
Ferric carboxymaltose (FCM) was TGA registered on 21 April 2011 for the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

4. Listing Requested and PBAC's View
Authority Required:
For treatment of iron deficiency anaemia, where oral iron preparations are not tolerated, ineffective or otherwise inappropriate.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
IDA is often a co-morbidity arising from a number of medical conditions, such as chronic kidney disease, inflammatory bowel disease, chronic heart failure, and women in the pregnant or postpartum period. Patients with IDA may have decreased functional ability, mental health or quality of life. In addition, IDA can amplify underlying chronic conditions thereby increasing the risk of hospitalisation and mortality.

Intravenous (IV) iron is considered when oral iron is not tolerated or is ineffective. IV iron will also be prescribed when a rapid increase in Hb level is clinically necessary to avoid physiological decompensation or blood transfusion (e.g. in patients with severe anaemia).

Ferric carboxymaltose is proposed as an alternative treatment to IV iron polymaltose (IP) for IDA patients who are intolerant or unresponsive to oral iron preparations and for patients who require rapid iron repletion.

6. Comparator
The submission nominated IV iron polymaltose as the main comparator. This was considered appropriate by the PBAC.

7. Clinical Trials
No head-to-head randomised controlled trials (RCTs) comparing FCM with IV IP were identified.

The submission presented the following clinical trials:

- Seven randomised trials comparing FCM to oral iron in IDA patients with chronic kidney disease, inflammatory bowel disease, postpartum women and women with heavy uterine bleeding: Trials 004, 008, 009, 001, 002/3, 011 and 017; and
- Four trials comparing IV IP with oral iron in IDA patients undergoing kidney transplant surgery, pregnant women and patients scheduled to have elective joint arthroplasty: Mudge 2012, Khalafallah 2010, Singh 1998 and Khalafallah 2012.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Proposed drug: FCM **Common reference: oral iron preparations**		
004 (005) Qunibi et al	A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis- dependent chronic kidney disease patients	*Nephrology Dialysis Transplantation* 2011;26 (5): 1599-1607
008 Kulnigg et al	A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial.	*American Journal of Gastroenterology* 2008; 103(5):1182-92
009 Breymann et al	Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia.	*International Journal of Gynaecology & Obstetrics* 2008; 101(1):67-7
001 Van Wyck et al	Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial.	*Obstetrics & Gynecology* 2007; 110(2 Pt 1): 267-78 (Erratum in *Obstetrics & Gynecology* 2008;111(4): 996
002/3 Van Wyck et al	Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial	*Transfusion* 2009; 49(12):2719-28
011 Seid et al	Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial	*American Journal of Obstetrics & Gynecology* 2008; 199(4):435.e1-7
Main comparator: IP		
Mudge et al	A randomized controlled trial of intravenous or oral iron for posttransplant anemia in kidney transplantation	*Transplantation* 2012; 93(8):822-6.
Khalafallah et al	A prospective randomized, controlled trial of intravenous versus oral iron for moderate iron deficiency anaemia of pregnancy	*Journal of Internal Medicine* 2010; 268(3):286-9
Singh et al	A comparison between intravenous iron polymaltose complex (Ferrum Hausmann) and oral ferrous fumarate in the treatment of iron deficiency anaemia in pregnancy	*European Journal of Haematology* 1998; 60(2):119-24
Khalafallah et al	A Prospective Randomized Controlled Trial to Assess the Effect of Intravenous versus Oral Iron Therapy in the Treatment of Orthopaedic Preoperative Anaemia	*Journal of Blood Disorders* & *Transfusion* 3(7):127

A comparison of trial populations in the FCM and IP studies is presented in the table below.

	Ferric Carboxymaltose	Iron Polymaltose
Kidney transplant recipients		Mudge 2012
Non-dialysis dependant chronic kidney disease	1VIT04004	
Pregnant women		Khalafallah 2010 Singh 1998
Post-partum	VIT-IV-CL-009 1VIT03001 1VIT06011	
Heavy uterine bleeding	1VIT4002/4003 1VIT07017	
Inflammatory bowel disease	VIT-IV-CL-008 1VIT07017	
Prior to joint surgery		Khalafallah 2012

The submission stated that a formal indirect comparison of FCM against IP, with oral iron preparations as the common comparator was not appropriate, given the heterogeneity in patients and outcomes.

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

The submission did not present any evidence allowing assessment of comparative effectiveness of FCM relative to IV IP. The submission presented the main efficacy outcomes of the mean change in Hb from baseline to the study end and the proportion of patients achieving target Hb levels across the seven randomised FCM trials in the following tables as evidence of the effectiveness of FCM over oral iron.

The changes in Hb from baseline to the end study is presented in the table below.

Changes in Hb from baseline to the end study across FCM trials

Trial ID		***Study period***	***Mean (SD) change in Hb (g/L)***		***p-value***	***Difference (FCM - FS) [95% CI] (g/L)***
			FCM	***FS***		
Trial 004		*8 weeks*	*N=133 10.5 (11.0)*	*N=84 7.0 (12.5)*	*0.034*	*3.5 [0, 7]*
Trial 008		*12 weeks*	*N=111 38.3 (19.5)*	*N=49 37.5 (19.6)*	*0.802*	*0.7 [-5.0, 6.5]*
Trial 009		*12 weeks*	*N=179 33.7 (17.7)*	*N=89 32.9 (16.9)*	*0.152*	*1.9 [-0.7, 4.5]*
Trial 001[a]		*6 weeks*	*N=159 42 (12.4)*	*N=157 33 (11.9)*	*<0.0001*	*9*[b]
Trial 002/3		*6 weeks*	*N=208 32.0 (14.6)*	*N=209 24.6(16.1)*	*<0.001*	*7.4*[b]
Trial 011		*6 weeks*	*N=137 40 (10.6)*	*N=143 34 (10.9)*	*<0.0001*	*6*[b]
Trial 017	*PP*	*4 weeks*[a]	*N=590 23.5 (12.3)*	*N=595 18.6 (12.7)*	*<0.001*	*4.9*[b]
	HUB	*4 weeks*[a]	*N=382 23.3 (13.3)*	*N=376 14.7 (13.3)*	*<0.001*	*8.6*[b]

CI = confidence interval; FCM = ferric carboxymaltose; FS = ferrous sulfate; Hb = haemoglobin; HUB = heavy uterine bleeding; PP = postpartum; SD = standard deviation

[a] Results reported in Trials 001 and 017 were changes from baseline to highest Hb levels;
[b] 95% CIs of the differences were not reported in the clinical study reports

The study periods varied across FCM trials. In trials with shorter treatment periods of 4 – 8 weeks (Trial 004, Trial 001, Trial 002/3, Trial 011 and Trial 017), statistically significantly higher increases in Hb levels from baseline to the study end were observed in patients treated with IV FCM compared to those in the oral iron arm.

In the other two trials with longer study periods (12 weeks), ie Trials 008 and 009, the differences in Hb changes between the two treatment arms were notably smaller than those reported in other trials (0.7 – 1.9g/L vs 3.5 – 9g/L). The 95% confidence intervals (CIs) of the differences in Trial 008 ([-5.0g/L, 6.5g/L]) and Trial 009 ([-0.7g/L, 4.5g/L]) were above the pre-specified non-inferiority margin of -5g/L, supporting a claim of non-inferiority.

Similar results were reported from analyses of the proportion of patients achieving treatment response:

The results of the response rates are presented in the table below.

Response rates during the study across FCM trials

Trial ID		Study period	Proportion of Hb responders n/N (%)		p-value	RD (FCM – FS) [95% CI]
			FCM	FS		
Trial 004[a]		8 weeks	87/144 (60.4%)	35/101 (34.7%)	< 0.001	25.7% [13.0%, 38.5%]
Trial 008		12 weeks	90/111 (81.1%)	40/49 (81.6%)	0.9343	-0.5%[b]
Trial 009		12 weeks	152/179 (84.9%)	73/89 (82.0%)	0.4115	2.9%[b]
Trial 001[a]		6 weeks	162/168 (96.4%)	159/169 (94.1%)	0.4433	2.3% [-2.2%, 6.9%]
Trial 002/3[a]		6 weeks	187/228 (82.0%)	139/225 (61.8%)	<0.001	20.2% [12.2%, 28.3%]
Trial 011[a]		6 weeks	127/139 (91.4%)	98/147 (66.7%)	<0.0001	24.7% [15.2%, 34.2%]
Trial 017	PP	4 weeks	233/342 (68.1%)	181/357 (50.7%)	<0.001	17.4%[b]
	HUB	4 weeks	195/331 (58.9%)	108/329 (32.8%)	<0.001	26.1%[b]

[a] Based on last observation carried forward method in which subjects who discontinued from the study prior to the end of the study were evaluated based on their last non-missing post-baseline value
[b] 95% CIs of the risk differences were not reported in the clinical study reports
CI = confidence interval; FCM = ferric carboxymaltose; FS = Ferrous sulfate; Hb = haemoglobin; HUB = heavy uterine bleeding; PP = postpartum; RD = risk difference

With regard to the four IP trials, Khalafallah 2010, Singh 1998 and Khalafallah 2012 demonstrated that IP, as monotherapy or in combination with oral iron, was superior to oral iron in terms of improving Hb levels. In contrast, Mudge 2012 found that the IV administration of FCM did not reduce the time to correction of anaemia compared with oral iron. However, the PBAC noted that this may be partially attributable to the insufficient drug dosage in the IP arm (500 mg).

The efficacy results are presented below.

Efficacy results from IP trials

Study	Outcomes	IP	Comparator	Comparison
Mudge 2012	Time to resolution of anaemia (Hb >110g/L)	12 days	21 days	HR: 1.22 [0.82, 1.83]
	Proportion of subjects requiring RBC transfusion	10%	18%	p = 0.24
Khalafallah 2010	Mean increase in Hb from baseline to delivery (g/L)	19.5	12	Difference: 6.6 [3.4, 9.8]
Singh 1998	Hb at recruitment (g/L), mean±SD	81 ± 0.1	86 ± 0.1	P<0.01
	Hb at 36 wk gestation (g/L), mean±SD,	110 ± 0.1	99 ± 0.2	Ratio of means[a]: 1.14 [1.08, 1.21]
	Hb at delivery (g/L), mean	118	112	NR
	Hb at 6 weeks postpartum (g/L), mean±SD	125 ± 0.1	119 ± 0.2	Ratio of means[a]: 1.05 [1.01, 1.09]
Khalafallah 2012	Hb immediate pre-operative (g/L), mean±SD	128 ± 11.1	118 ± 9.2	p = 0.01
	RBC transfused (units), mean±SD	1.5 ± 0.58	2.2 ± 0.83	p = 0.09
	Hb 6 weeks after surgery (g/L), mean±SD	120 ± 13.8	108 ± 11.2	p = 0.01

Hb = haemoglobin; HR = hazard ratio; IP = iron polymaltose; RBC = red blood cell; SD = standard deviation
[a] Results were adjusted for duration of treatment and baseline outcome measures.

In terms of comparative harms, the submission did not present any evidence formally comparing the safety of FCM compared with IV IP.

The submission claimed that FCM had low rates of hypersensitivity reactions, and delayed infusion reactions.

Across the seven FCM trials, treatment emergent adverse events (TEAEs) were broadly comparable between groups. The PBAC agreed that the low incidence rates of serious TEAEs (0%-9.7%) and TEAEs leading to treatment withdrawal (0%-7.9%) reported across oral iron arms implied that trial subjects tolerated oral iron well and so differed from the proposed PBS 'oral iron intolerant' population.

Hypersensitivity was rare among FCM-treated patients, with incidences ≤0.5% across trials. Four deaths were reported in patients receiving FCM treatment; whereas no subjects in the oral iron arms died during the studies. None of the deaths reported was considered to be related to the study medication.

Safety analyses were conducted for the Periodic Safety Update Report (PSUR) for FCM (for the period 12/2010 to 06/2011). The analyses showed:

- lower rates of hypersensitivity related events in the FCM arm of the analysed clinical trials (0.13%) and during post-marketing (0.08%) than the hypersensitivity event risk for the respective background populations (1.2% – 16.8%); and
- lower incidences of fatal events in the FCM arm of the analysed clinical trials (0.49%) and during post-marketing (0.003%) compared with the mortality risk for the respective background populations (up to 20% – 52%).

The PBAC also noted that the "respective background populations" as used in the PSUR was not described in the submission and no detailed information of the above analyses was provided and the validity of results could not be assessed.

Minimal safety data reported in the four IP trials showed that it was well tolerated among trial subjects.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that FCM is non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety to IV IP.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost analysis based on the claim of non-inferior efficacy and safety between FCM and IV IP. The submission provided a modelled assessment of the comparative treatment and administrative costs associated with total iron replenishment using FCM or IP. The model was structured as a simple decision tree in which patients received either FCM or IP in various healthcare settings, with associated drug acquisition and administration costs.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated with FCM per year was estimated in the submission to be between 10,000 – 50,000 in Year 5, at an estimated net cost per year to the R/PBS of between $10-30 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended listing of ferric carboxymaltose on the PBS as unrestricted benefit, which is consistent with the nominated comparator, iron polymaltose (IP), for the treatment of iron deficiency anaemia. Listing should be on a cost-minimisation basis with iron polymaltose, with equi-effective doses based on a 1:1 ratio of iron delivered by the formulations.

The PBAC accepted that IP was an appropriate comparator, however, the PBAC noted that the requested restriction for FCM as an authority required benefit was not consistent with the comparator, IP which is currently PBS listed as unrestricted benefit. The PBAC further noted that the populations sought in the requested restriction were not consistent with those in the clinical trials presented.

The PBAC considered that the submission's claim of non-inferior comparative effectiveness and comparative safety compared with IV IP was not sufficiently supported by the evidence presented due to the lack of appropriate comparative trials of FCM and IV IP. The PBAC noted that there was little overlap of measured outcomes across the trials. The PBAC noted

that although clinical trials investigating FCM versus oral iron and IP versus oral iron were identified, no meaningful formal indirect comparison between the two trial sets could be performed. The comparative effectiveness and safety of FCM relative to IV IP, therefore, could not be quantitatively evaluated.

The PBAC noted that the trials were designed as non-inferiority trials, and that there were statistically significantly higher increases in Hb levels from baseline to the study end observed in FCM treated group compared with the oral iron treated group, however this observation could only be seen in the trials with shorter treatment periods (4-8 weeks), and not in those with longer study periods (12 weeks). From analyses of the proportion of patients achieving treatment response, the PBAC noted that although faster response to treatment was observed with FCM than with oral iron, no difference was observed in the longer term.

Overall, the PBAC considered that the comparative safety between FCM and IP was difficult to assess, based on the limited data provided.

The submission presented a cost analysis based on the claim of non-inferior efficacy and safety. However, there were no equi-effective doses between FCM and IP derived from the trial evidence. The PBAC recommended that in the absence of the evidence, it was appropriate to determine the equi-effective dose on a 1:1 basis based on the iron content of FCM and IP; and that this view was supported by the sponsor in its Pre-Sub Committee Response (PSCR).

The PBAC noted that in the trials, both FCM and IP were dosed using Ganzoni formula, however, in the economic evaluation dose requirements were calculated at an individual level, with FCM dosed according to a new simplified 2x2 table and IP dosed according to the established Ganzoni formula. The PBAC also noted that there were no equi-effective doses provided with the 'simplified dosing' and the IP dosing.

The PBAC considered there were a number of uncertainties associated with assumptions made in the economic model including:

- In the non-hospital setting, the assumption of 95 % of patients were treated with the required dose of IV IP under the care of a specialist; and only 5 % received a suboptimal dose (<500 mg) by intra-muscular (IM) injection in general practice. The assumption of little use of IP, given by IM injection, was considered to be an underestimate.
- In the public hospital setting, the assumption of 80% of patients were admitted to the ward to receive IV IP; and no patients required a hospital admission to receive FCM. This assumption was considered unjustified as administration in public hospitals likely to be dictated by local/State protocols etc.
- The assumption that all patients admitted to hospitals incur a stand-alone hospitalisation cost would over-estimate the administration costs of IV IP.
- Cost comparison presented was based on the 500 mg vial of FCM, and the 100 mg vial of FCM was not considered.

The submission presented a one-way sensitivity analysis, which indicated that the model was sensitive to variations in the cost of public hospital-based administration. As noted above, the cost of public hospital administration of IP was over-estimated, and consequently a net

incremental cost for FCM treatment compared with IP treatment was considered likely by the PBAC.

The PBAC considered that the presented economic model was over-complicated and that there were a number of uncertainties associated with the assumptions that were made in the model. The PBAC hence considered that a cost-minimisation analysis on the basis of a 1:1 ratio of iron delivered by the formulations would have been more appropriate, given the non-inferiority clinical claim made between FCM and IV IP.

The PBAC considered that the estimation of number of patients was underestimated. Given the shorter administration time, the uptake of this product may be greater than anticipated, also there is a high potential for leakage.

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.

The PBAC recommended that ferric carboxymaltose is suitable for inclusion in the medicines for prescribing by nurse practitioners within collaborative arrangements.

The PBAC noted the consumer comments received in relation to the submission.

Recommendation:
Recommended

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
FERRIC CARBOXYMALTOSE Injection 100 mg (iron) in 2 mL	2	1	Ferinject	ViforPharma Pty Ltd
FERRIC CARBOXYMALTOSE Injection 500 mg (iron) in10 mL	2	1	Ferinject	ViforPharma Pty Ltd

Condition/Indication:	Iron deficiency anaemia
Restriction:	Unrestricted

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Vifor Pharma will continue to work with the PBAC to resolve the issues in order to make ferric carboxymaltose available on the PBS to patients with iron deficiency anaemia.