

5.06 FERRIC DERISOMALTOSE, Injection 500 mg (iron) in 5 mL, Monofer[®], Pfizer Australia Pty Ltd

1 Purpose of Application

- 1.1 The submission requested a Section 85 General Schedule, Unrestricted listing for ferric derisomaltose for treatment of iron deficiency anaemia when treatment with oral iron is ineffective or not tolerated. This was the first application to the PBAC for ferric derisomaltose.
- 1.2 The submission presented a cost-minimisation analysis compared to the main comparator, ferric carboxymaltose.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adult patients with iron deficiency anaemia, when treatment with oral iron is ineffective or unsuitable.
Intervention	Ferric derisomaltose delivered by intravenous infusion. Dose is determined by calculation of cumulative iron need using either the Ganzoni formula ^a or simplified dosing table ^b .
Comparator	Ferric carboxymaltose delivered by intravenous infusion. Dose is determined by calculation of cumulative iron need using either the Ganzoni formula ^a or simplified dosing table ^c .
Outcomes	Improvement in Hb status, as measured by: - change in Hb from baseline; or - proportion of responders (defined as an increase in Hb of ≥ 2.0 g/dL, or normalisation of Hb).
Clinical claim	In patients with iron deficiency anaemia, treatment with ferric derisomaltose is non-inferior to ferric carboxymaltose in improving Hb levels. In terms of safety, ferric derisomaltose is non-inferior to ferric carboxymaltose. The equi-effective dose is a ratio of elemental iron of 1 mg: 1 mg.

Source: Table 1-1, p3 of the submission

g/dL = grams per decilitre; g/L = grams per litre; Hb = haemoglobin

^a Iron need = body weight (kg) x (Target Hb (g/L) – Actual Hb (g/L)) x 0.24 + Iron for iron stores (mg)

^b Anaemia with Hb ≥ 100 g/L patients would be given 1000 mg of iron if bodyweight is 50 kg to <70 kg or 1500 mg of iron if bodyweight ≥ 70 kg; anaemia with Hb <100 g/L patients would be given 1500 mg of iron if bodyweight is 50kg to <70 kg or 2000 mg of iron if bodyweight is ≥ 70 kg.

^c Anaemia with Hb ≥ 100 g/L patients would be given 1000 mg of iron if bodyweight is 35 kg to <70 kg or 1500 mg of iron if bodyweight ≥ 70 kg; anaemia with Hb <100 g/L patients would be given 1500 mg of iron if bodyweight is 50kg to <70 kg or 2000 mg of iron if bodyweight is ≥ 70 kg.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IRON Iron (as ferric derisomaltose) 500 mg/5 mL injection, 1 x 5 mL vial	2	1	\$SPA (TBA) \$307.49	Monofer [®] Pfizer Australia

Max = maximum; Qty = quantity; Rpts = repeats; SPA = Special Price Arrangement; TBA = to be advised based on main comparator, ferric carboxymaltose

- 2.1 The submission acknowledged that the main comparator, ferric carboxymaltose, is subject to a confidential Special Pricing Arrangement (SPA) and was willing to adopt an equivalent SPA to ensure the cost-minimisation framework was maintained.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Ferric derisomaltose was approved by the TGA on 4 December 2017 for:

“The treatment of iron deficiency in adults, under the following conditions:

- When oral iron preparations are ineffective or cannot be used; or
- Where there is a clinical need to deliver iron rapidly; and

The diagnosis must be based on laboratory tests.”

4 Population and disease

- 4.1 The target PBS population proposed by the submission for treatment with ferric derisomaltose were patients with iron deficiency anaemia, when treatment with oral iron is ineffective or not tolerated.
- 4.2 Populations at high risk of iron deficiency anaemia include post-partum women and patients with chronic kidney disease or inflammatory bowel diseases.
- 4.3 Ferric derisomaltose is an intravenous (IV) iron, suitable for fast infusion and administration in primary care and other non-hospital settings. Ferric derisomaltose is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles, which enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron. This allows for flexible dosing, which includes high and rapid dosing of up to 1500 mg in 30 minutes or less.
- 4.4 The submission stated that oral iron remains the first-line treatment of iron deficiency anaemia, with IV irons such as ferric carboxymaltose, iron polymaltose and iron sucrose, appropriate in specific scenarios. The PBAC considered that this was reasonable.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission proposed that ferric derisomaltose would have the same place in therapy as ferric carboxymaltose. The main arguments provided in support of this nomination by the submission were that:
- ferric carboxymaltose was a pharmacological analogue of ferric derisomaltose;
 - ferric carboxymaltose was the most widely used IV iron, with at least 75% market share; and
 - due to the comparable administration requirements and infusion time of ferric carboxymaltose, it would be the therapy most likely to be replaced by the PBS listing of ferric derisomaltose.
- 5.2 There are three PBS listed IV iron formulations: iron polymaltose, iron sucrose and ferric carboxymaltose. The submission considered that the infusion time and administration requirements meant that these therapies could not be considered interchangeable. Iron polymaltose is required to be infused over a five hour period and would therefore not be suitable for administration in non-hospital settings. However, patients treated with iron polymaltose may receive up to 2500 mg of iron in a single infusion. Iron sucrose is administered during dialysis and is TGA restricted to patients undergoing haemodialysis and receiving erythropoietin stimulating agents. In comparison, ferric carboxymaltose is a fast-infusion iron formulation that can be administered in a single infusion up to 1000 mg in 20 minutes, and would therefore be suitable for administration in non-hospital settings.
- 5.3 The nominated comparator was reasonable; however it should be noted that ferric derisomaltose could be used as a substitute to iron polymaltose in patients who require rapid high dosing of iron (up to 1500 mg). Ferric derisomaltose could also be a substitute for iron sucrose in haemodialysis patients, especially as a recent clinical trial has found ferric derisomaltose to have comparable safety and efficacy to iron sucrose in haemodialysis patients. Therefore, iron polymaltose and iron sucrose may be appropriate comparators in these patient groups. In its Pre-Sub-Committee Response (PSCR), the sponsor argued that iron sucrose and iron polymaltose should not be considered relevant comparators for ferric derisomaltose due to differences in administration requirements, infusion time, specific dose restrictions and TGA indications. The ESC noted the results of a utilisation review of ferric carboxymaltose performed in 2017 by the Drug Utilisation Sub Committee (DUSC) indicating that ferric carboxymaltose holds the majority of the market share with use of iron polymaltose low and negligible use of iron sucrose. The ESC agreed with the sponsor that iron sucrose was not an appropriate comparator due to differences in administration requirements, dosing and TGA indication. The ESC noted that administration requirements mean that unless administered intramuscularly (up to 200 mg), iron polymaltose is not suitable for administration in the non-hospital setting. As such, the ESC also agreed with the sponsor that iron polymaltose was not

an appropriate comparator. The PBAC agreed with the ESC and further considered that, due to similarities in administration, dosing and TGA indications, ferric derisomaltose would most likely replace ferric carboxymaltose in practice, and therefore ferric carboxymaltose was the appropriate comparator.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on an indirect comparison and included four randomised controlled trials (RCT). Ferric derisomaltose (PROVIDE) was compared with ferric carboxymaltose (FERGICor, Mahey 2016 and REPAIR-IDA) via the common comparator, iron sucrose.

6.4 During the evaluation, it was considered that iron sucrose was an appropriate comparator for ferric derisomaltose in haemodialysis patients. The evaluation identified one RCT, which was excluded by the submission, which compared ferric derisomaltose to iron sucrose in patients undergoing haemodialysis (P-Monofer-CKD-03). However, the PBAC considered that ferric carboxymaltose was the only appropriate comparator (see paragraph 5.3).

6.5 Details of the trials presented in the submission and by the evaluation are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ferric derisomaltose		
PROVIDE (NCT02130063)	A Phase III, Randomised, Open-Label, Comparative Study of Intravenous Iron Isomaltoside 1000 (Monofer®) and Iron Sucrose in Subjects with Iron Deficiency Anaemia and who are Intolerant or Unresponsive to Oral Iron Therapy or who need Iron rapidly. Clinical Study Report. Derman R, Roman E, Modiano MR et al. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anaemia.	February 2016 American Journal of Hematology 2017; 92(3):286-291
P-Monofer-CKD-03 (NCT01222884)	Bhandari S, Kalra P, Kothari J et al. A randomized, open-label trial of iron isomaltoside 1000 (Monofer®) compared with iron sucrose (Venofer®) as maintenance therapy in haemodialysis patients.	Nephrol Dial Transplant 2015; 30:1577-1589
Ferric carboxymaltose		
FERGICor (NCT00810030)	Evstatiev R, Marteau P, Iqbal T, et al. FERGICor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anaemia in inflammatory bowel disease.	American Journal of Obstetrics and Gynecology 2008; 141(3):846-853
REPAIR-IDA (NCT00981045)	Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anaemia and impaired renal function: the REPAIR-IDA trial.	Nephrol Dial Transplant 2014; 29(4):833-842
Mahey (2016) (CTRI/2015/09/006224)	Mahey R, Kriplani A, Mogili KD, et al. Randomized controlled trial comparing ferric carboxymaltose and iron sucrose for treatment of iron deficiency anaemia due to abnormal uterine bleeding.	International Journal of Gynaecology and Obstetrics 2016, 133(1):43-48

Source: Compiled during the evaluation from Table 2-5, pp11-12 of the submission and Bhandari (2015)

6.6 The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in indirect comparison
Ferric derisomaltose vs iron sucrose						
PROVIDE	491	R, OL, NI 5 weeks	High	Various	% Hb responders; Δ Hb from baseline; safety	Yes
P-Monofer-CKD-03	341	R, OL, NI 6 weeks	High	HD-CKD	% Hb responders; Δ Hb from baseline; safety	Not used in the indirect comparison with FCM as IS was considered the appropriate comparator in haemodialysis patients.
Ferric carboxymaltose vs iron sucrose						
FERGICor	475	R, OL, NI 12 weeks	High	Gastro: IBD	% Hb responders; safety	Yes
REPAIR-IDA	2520	R, OL, NI 8 weeks	High	NDD-CKD	% Hb responders; Δ Hb from baseline; safety	
Mahey (2016)	58	R, OL, NI 12 weeks	High	Gynae	% Hb responders; Δ Hb from baseline; safety	
Meta-analysis	3053	Included FERGICor, REPAIR-IDA, Mahey (2016) for efficacy outcomes: % Hb responders and Δ Hb from baseline				

Source: Compiled during the evaluation from Section 2, pp 1-60 of the submission and Bhandari (2015)

gastro = gastrointestinal; gynae = gynaecology; Hb = haemoglobin; HD-CKD = haemodialysis dependent chronic kidney disease; IBD = inflammatory bowel disease; IS = iron sucrose; NDD-CKD = non-dialysis dependent chronic kidney disease; NI = non-inferiority; OL = open label; R = randomised;

- 6.7 The PBAC noted that overall, the trials had a high risk of bias as all were open label and, with the exception of Mahey (2016), all were sponsored by pharmaceutical companies.
- 6.8 Patients in the intervention arms of PROVIDE (i.e. ferric derisomaltose), FERGICor and REPAIR-IDA (i.e. ferric carboxymaltose) received significantly higher doses of iron than patients in the comparator arms (i.e. iron sucrose) of the trials. Therefore, the results from PROVIDE, FERGICor and REPAIR-IDA were biased in favour of ferric derisomaltose and ferric carboxymaltose.
- 6.9 The PBAC considered that the key differences between the trials that may impact on the transitivity were:
- Patients in the ferric derisomaltose arm of PROVIDE received higher doses of iron than patients in the ferric carboxymaltose arms of FERGICor and REPAIR-IDA (mean doses of 1640 mg vs 1377 mg and 1464 mg respectively);
 - Patients in PROVIDE had a lower baseline haemoglobin (Hb) level (mean Hb = 9.4 g/dL) than patients in FERGICor and REPAIR-IDA (mean Hb = 10.2 g/dL and 10.3 g/dL respectively). Patients in Mahey (2016) had the lowest baseline Hb levels (mean Hb = 7.6 g/dL);
 - The Hb response rate in the common reference arm of REPAIR-IDA was lower

than the response rate in the common reference arm of PROVIDE (41% vs 52%), whilst the response rate was higher in the common reference arm of Mahey (2016) (66%); and

- The results from the studies included in the network analysis were reported at different time points: results for ferric derisomaltose were reported at five weeks (PROVIDE) and for ferric carboxymaltose at eight (REPAIR-IDA) and 12 weeks (FERGICor and Mahey (2016)). As higher doses of iron may be given in a single infusion with ferric derisomaltose (up to 1500 mg) and ferric carboxymaltose (up to 1000 mg) than with iron sucrose (up to 200 mg in the trials), this would result in a faster response time for patients treated with ferric derisomaltose and ferric carboxymaltose compared to patients treated with iron sucrose. However, over time Hb levels would converge as patients treated with iron sucrose would eventually receive equivalent doses of iron. The shorter reporting time points in PROVIDE likely biased the results in favour of ferric derisomaltose.

Comparative effectiveness

6.10 The primary outcomes for each of the included trials were the:

- proportion of patients achieving a clinically relevant Hb response (defined in most studies as ≥ 2.0 g/dL increase from baseline); and
- change in Hb levels from baseline (g/dL).

6.11 The key efficacy outcomes presented by the submission were appropriate and consistent with the outcomes presented in the ferric carboxymaltose submission (paragraph 8, March 2013 Public Summary Document (PSD) ferric carboxymaltose).

6.12 The submission applied non-inferiority (NI) margins of -0.5 g/dL for change in Hb from baseline and -12.5% for the difference in proportion of Hb responders (i.e. increase in Hb of ≥ 2 g/dL). The submission stated that these NI margins were applied as they had previously been accepted by the PBAC in consideration of ferric carboxymaltose (paragraph 8, March 2013 PSD ferric carboxymaltose). The proposed NI margins were appropriate.

Ferric derisomaltose vs ferric carboxymaltose (indirect comparison)

6.13 Table 4 presents the results of the indirect comparison between ferric derisomaltose and ferric carboxymaltose for the outcome: proportion of patients achieving a clinically relevant Hb response at the primary endpoint.

Table 4: Results of the indirect comparison: proportion of patients achieving a clinically relevant Hb response at the primary endpoint

Trial	Primary endpoint	Proportion of Hb responders (n/N)			Risk difference (95% CI)
		FD	IS	FCM	
Ferric derisomaltose vs iron sucrose					
PROVIDE	5 weeks	226 / 330 (69%)	83/161 (52%)	-	16.7% (7.5; 25.7)
Ferric carboxymaltose vs iron sucrose					
FERGICor	12 weeks	-	150/240 (66%)	118/235 (54%)	12.2% (3.1; 20.1)
REPAIR-IDA	8 weeks	-	607/1249 (49%)	510/1244 (41%)	7.6% (3.6; 11.6)
Mahey (2016)	12 weeks	-	22/29 (75%)	19/29 (66%)	10.3% (-12.9; 36.6)
Pooled Result: FCM vs IS (Chi ² p-value =0.63; I ² = 0%)					8.0% (5.0; 12.0)
Indirect Comparison (95% CI): FD vs FCM					8.5% (-1.3; 18.3)
NI margin					-12.5%

Source: Table 2-17, p29; Tables 2-19-2-20; pp31-32; Table 2-21, p32, Figure 2.8, p46 and Table 2-36, p49 of the submission
 CI = confidence interval; FCM = ferric carboxymaltose; FD = ferric derisomaltose; Hb = haemoglobin; IS = iron sucrose; n = number of participants with event; N = total participants in group; **bold** = statistically significant; *italics* = calculated during evaluation

6.14 The risk difference in response rates between ferric derisomaltose and ferric carboxymaltose was 8.5% (95% confidence interval (CI): -1.3%; 18.3%). As the lower bound of the 95% CI was above the NI margin of -12.5%, the submission claimed non-inferiority for ferric derisomaltose. This may not be reasonable given the high level of clinical heterogeneity between trials and the transitivity issues identified by the evaluation.

6.15 Table 5 presents the results of the indirect comparison between ferric derisomaltose and ferric carboxymaltose for the outcome: mean change in Hb level from baseline at the primary endpoint.

Table 5: Results of the indirect comparison: mean change in Hb (g/dL) level from baseline at the primary endpoint

Trial	Primary Endpoint	Mean change in Hb level (g/dL) from baseline (SD)			Mean difference, g/dL (95% CI)
		FD	IS	FCM	
Ferric derisomaltose vs iron sucrose					
PROVIDE	5 weeks	N = 322 2.52 (1.41)	N = 155 2.05 (1.27)		0.46 (0.30; 0.62)
Ferric carboxymaltose vs iron sucrose					
REPAIR-IDA	8 weeks		N = 1244 0.92 (0.92)	N = 1249 1.13 (1.04)	0.21 (0.13; 0.28)
Mahey (2016)	12 weeks		N = 29 NR	N = 29 NR	0.29 (-0.26; 0.84)
Pooled Result: FCM vs IS (Chi ² p-value =0.86; I ² = 0%)					0.21 (0.13; 0.29)
Indirect WMD (95% CI): FD vs FCM					0.25 (0.07; 0.43)
NI margin					-0.5 g/dL

Source: Table 2-18, p30; Table 2-20, p32; Table 2-23, p33, Figure 2.7, p46 and Table 2-36, p49 of the submission
 CI = confidence interval; FCM = ferric carboxymaltose; FD = ferric derisomaltose; g/dL = grams per decilitre; Hb = haemoglobin; IS = iron sucrose; N = number of participants reporting data; NI = non-inferiority; SD = standard deviation; WMD = weighted mean difference; **bold** = statistically significant

6.16 The result of the indirect comparison for the mean difference in Hb from baseline was 0.25 g/dL (95% CI: 0.07; 0.43). As the lower bound of the 95% CI was below the NI threshold of -0.5g/dL the submission claimed non-inferiority. Again, this may not

be reasonable given the high level of clinical heterogeneity between trials and the transitivity issues identified by the evaluation.

Ferric derisomaltose vs iron sucrose in haemodialysis patients (direct comparison)

6.17 Table 6 presents the results of the primary outcome from trial P-Monofer-CKD-03: the proportion of patients with Hb in the target range of 9.5 and 12.5 g/dL at 6 weeks follow-up.

Table 6: Trial results from P-Monofer-CKD-03 for the proportion of patients with Hb in the target range of 9.5 and 12.5 g/dL at 6 weeks follow-up

Proportion of responders		RD (95% CI)
Ferric derisomaltose ^a n/N (%)	Iron sucrose n/N (%)	
187/226 (83%)	95/115 (83%)	1.0% (-7.4; 9.4)

Source: Compiled from text, p1581 and Figure 5, p1582 of Bhandari (2015)

CI = confidence interval; g/dL =grams per decilitre; Hb = haemoglobin; n = number of participants with event; N = total participants in group

RD = risk difference; italics = extracted during evaluation

^a Trial results of the ferric derisomaltose arms (single or split dose) were combined

6.18 The results demonstrated ferric derisomaltose (split or single dose) to be non-inferior to iron sucrose for the maintenance of Hb in patients undergoing haemodialysis.

6.19 Table 7 presents the results of the secondary outcome from trial P-Monofer-CKD-03: the mean change in Hb from baseline at 6 weeks follow-up.

Table 7: Trial results from P-Monofer-CKD-03 for the outcome: mean change in Hb (g/dL) from baseline

Ferric derisomaltose ^a			Iron Sucrose			Mean difference (95% CI)
N	Mean at baseline (SD)	Mean change	N	Mean at baseline (SD)	Mean change	
226	11.20 (0.83)	-0.01	115	11.08 (0.93)	-0.03	0.02 (-0.20; 0.25)

Source: Compiled from Table 4, p 1583 of Bhandari (2015)

CI = confidence interval; g/dL =grams per decilitre; Hb = haemoglobin; N = total number of patients; SD = standard deviation

^a Trial results of the ferric derisomaltose arms (single or split dose) were combined

6.20 The results showed no statistically significant changes from baseline at 6 weeks between patients treated with ferric derisomaltose (single or split dose) and patients treated with iron sucrose.

6.21 Overall, the results suggested that ferric derisomaltose was non-inferior to iron sucrose in patients undergoing haemodialysis, as the lower bounds of the 95% CIs were above the NI margins for the mean change in Hb from baseline (NI margin = -0.5g/dL) at 6 weeks follow-up.

Comparative harms

Ferric derisomaltose vs ferric carboxymaltose (indirect comparison)

6.22 The submission presented a naïve indirect comparison of adverse events between ferric derisomaltose and ferric carboxymaltose (Table 8), as a formal indirect comparison was not possible. The PBAC considered that this was reasonable.

Table 8: Naïve comparison of safety reported in the trials between ferric derisomaltose and ferric carboxymaltose ^a

Trial	PROVIDE ^b	FERGICor	REPAIR-IDA ^b
Intervention	FD	FCM	FCM
Safety Analysis Set, N	333	244	1276
Any adverse event, n (%)	144 (43%)	34 (14%)	-
Serious adverse events, n (%)	11 (3%)	-	202 (16%)
- Leading to death, n (%)	1 (<1%)	-	-
- Leading to dose reduction, n (%)	3 (1%)	-	-
- Leading to drug withdrawal, n (%)	10 (3%)	7 (3%)	-
Hypersensitivity ^c	31 (9%)	4 (2%)	9 (1%)

Source: Table 2-26, Table 2-27, Table 2-35 and compiled from text, pp35-47 of the submission

FCM = ferric carboxymaltose; FD = ferric derisomaltose; n = number of participants with event; N = total participants in group

^a Only limited safety data was reported by Mahey (2016) and was therefore not presented

^b Trial reported treatment emergent adverse events

^c Hypersensitivity events were defined differently across the trials and were not comparable

6.23 Patients treated with ferric derisomaltose reported a higher number of adverse events (43% vs 14%) and rates of hypersensitivity (9% vs 1 to 2%) than patients treated with ferric carboxymaltose. However, the number of serious adverse events was lower (3% vs 16%) in the ferric derisomaltose arm. These differences were likely due to the patient groups enrolled in each of the trials. PROVIDE predominately enrolled patients with iron deficiency anaemia caused by gastrointestinal and gynaecological etiologies, whilst REPAIR-IDA exclusively enrolled patients with chronic kidney disease.

6.24 Overall, the submission's claim of non-inferior safety was uncertain as the evidence presented by the submission was based on a naïve indirect comparison between heterogeneous patient populations and only limited data was provided by the publications.

Ferric derisomaltose vs iron sucrose in haemodialysis patients (direct comparison)

6.25 Table 9 summarises the overall safety profile of ferric derisomaltose compared with iron sucrose in patients undergoing haemodialysis in the P-Monofer-CKD trial.

Table 9: Summary of key adverse events in P-Monofer-CKD trial

	FD (single dose)	FD (split dose)	IS	FD (single dose) vs IS RD (95% CI)	FD (split dose) vs IS RD (95% CI)
N	114	116	114		
AE, n (%)	51 (45%)	59 (51%)	47 (41%)	4% (-9%, 16%)	11% (-2%, 23%)
ARD, n (%)	6 (5%)	6 (5%)	3 (3%)	3% (-2%, 8%)	3% (-2%, 8%)
Serious AE, n (%)	9 (8%)	13 (11%)	6 (5%)	3% (-4%, 9%)	6% (-1%, 13%)
Serious ARDs (%)	1 (1<%)	0	2 (2%)	1% (-4%, 2%)	-2% (-4%, 1%)

Source: Table 8, p1587 of Bhandari (2015)

AE = adverse event, ARD = adverse drug reaction; CI = confidence interval; FD = ferric derisomaltose; IS = iron sucrose; n = number of participants with event; N = total participants in group RD = risk difference.

6.26 While the number of adverse events (45% and 51% vs 41%) and serious adverse events (8% and 11% vs 5%) were all higher in the ferric derisomaltose arms than the iron sucrose arm, these differences were not statistically significant. The results suggested that ferric derisomaltose had non-inferior safety to iron sucrose in haemodialysis patients.

Clinical claim

Ferric derisomaltose vs ferric carboxymaltose (indirect comparison)

- 6.27 The submission described ferric derisomaltose as non-inferior in terms of efficacy compared with ferric carboxymaltose and non-inferior in terms of safety compared to ferric carboxymaltose for the treatment of iron deficiency anaemia.
- 6.28 Overall, the submission’s claim of non-inferior efficacy and safety for ferric derisomaltose compared to ferric carboxymaltose was not supported by the evidence as there was considerable uncertainty in the results due to clinical heterogeneity between trials and transitivity issues associated with the indirect comparison. The PSCR acknowledged the transitivity issues associated with the indirect comparison and noted that the results of the indirect comparison did meet the margins previously accepted by the PBAC for assessment of non-inferiority. The ESC considered that this may not be reasonable given the high level of clinical heterogeneity between trials and the transitivity issues identified by the evaluation. The pre-PBAC response requested that the clinical claims be considered in the context of the broader knowledge of the use of IV iron in the management of iron deficiency anaemia. The pre-PBAC response stated that IV iron delivers a dose of elemental iron to satisfy a measured deficit in an individual patient and it is generally accepted that in equivalent doses, all IV iron compounds are likely to lead to comparable efficacy as measured by the ability to increase Hb. The pre-PBAC response stated that this premise is consistent with the Therapeutic Relativity statements (PBS 2018) that IV iron formulations are equi-effective on a “per mg of elemental iron” basis and that national (NBA 2015, Pasricha et al 2010, eTG 2018) and international (Goddard et al 2011) treatment guidelines do not distinguish between IV irons for the purposes of dose calculation.

6.29 The PBAC considered that on balance, the claim of non-inferior comparative effectiveness and safety was reasonable. The PBAC noted that heterogeneity and transitivity issues between the trials made it difficult to draw accurate conclusions. However, the PBAC considered that the results of the direct comparison between ferric derisomaltose versus iron sucrose further supported the premise that in equivalent doses, IV iron compounds are likely to lead to comparable efficacy.

Ferric derisomaltose vs iron sucrose in haemodialysis patients (direct comparison)

6.30 The results from P-Monofer-CKD demonstrated ferric derisomaltose to have non-inferior efficacy to iron sucrose for the maintenance of Hb levels in haemodialysis patients.

6.31 The results suggested that ferric derisomaltose had non-inferior safety to iron sucrose in haemodialysis patients.

6.32 The PBAC considered the claim that ferric derisomaltose is non-inferior in terms of comparative effectiveness and safety to iron sucrose was reasonable.

Economic analysis

6.33 For the economic evaluation the submission presented a cost-minimisation approach compared to ferric carboxymaltose. The PBAC considered that this was appropriate.

Table 10: Key components and assumptions of the cost-minimisation analysis presented by the submission

Component	Claim or assumption
Therapeutic claim: efficacy	Non-inferior efficacy for Hb responder rate and change in Hb from baseline
Therapeutic claim: safety	Non-inferior safety with similar profile of adverse events
Evidence base	Indirect comparison based on PROVIDE and; a meta-analysis of Mahey (2016), REPAIR-IDA and FERGICor
Equi-effective doses	1 mg FD = 1 mg FCM
Direct medicine costs	1000 mg FD = 1000 mg FCM = \$272.00 (AEMP)
Other costs or cost offsets	None. Although the submission noted that at some doses higher than 1000 mg, treatment with FD will involve fewer infusions (not quantified).

Source: Section 3.1, p62 of the submission

AEMP = approved ex-manufacturer price; FCM = ferric carboxymaltose; FD = ferric derisomaltose; Hb = haemoglobin

6.34 The submission applied an equi-effective dose based on a 1 mg: 1 mg of iron delivered. The submission’s reasoning was that the PBAC had previously accepted an equi-effective dose of 1 mg: 1 mg for ferric carboxymaltose, which was based on a naïve indirect comparison with iron polymaltose (paragraph 12, March 2013 PSD ferric carboxymaltose). The submission also noted the advice of the Therapeutic Relatively statements (PBS 2018) which states that ferric carboxymaltose, iron polymaltose and iron sucrose equi-effective on a “per mg of elemental iron” basis. The submission considered it was reasonable to extend this to include ferric derisomaltose. However, the PBAC Version 5 Guidelines (p98) recommends trial data be used to estimate the equi-effective dose.

6.35 A comparison of trial doses showed that patients in the ferric derisomaltose treatment arm of PROVIDE received higher doses of iron than patients in the ferric

carboxymaltose treatment arms. An equi-effective dose of ferric derisomaltose to ferric carboxymaltose of 1.15 mg: 1 mg of iron delivered, based on trial data was calculated by the evaluation.

- 6.36 The PSCR rejected the equi-effective dose of 1.15 mg ferric derisomaltose to 1 mg ferric carboxymaltose as calculated in the evaluation, and reiterated the reasoning outlined in paragraph 6.34 as to why it believed the equi-effective dose should be 1 mg: 1 mg.
- 6.37 The ESC considered that an equi-effective dose of 1 mg: 1 mg was reasonable, as in practice ferric carboxymaltose is commonly administered in amounts of 500 mg or 1000 mg rather than by smaller incremental amounts. The ESC considered a similar approach would be expected for ferric derisomaltose. The PBAC agreed with the ESC that an equi-effective dose of 1 mg: 1 mg was reasonable.
- 6.38 The submission stated that ferric derisomaltose will have the same overall cost of treatment as ferric carboxymaltose with an approved ex-manufacture price (AEMP) of \$272 per 1000 mg, assuming an equi-effective dose of 1 mg (ferric derisomaltose): 1 mg (ferric carboxymaltose).

Drug cost/patient/course = \$307.49

- 6.39 The cost per patient per course of treatment with ferric derisomaltose, assuming the most commonly prescribed dose (based on the 2017 DUSC utilisation review) of 1000 mg was \$307.49 (Published Dispensed Price for Maximum Quantity (DPMQ)). Based on the mean dose in the pivotal trial (PROVIDE; 1640 mg) the cost per patient per course would be \$614.98 (based on DPMQ of \$307.49). The PBAC noted that the maximum dose per IV infusion for ferric derisomaltose (1500 mg) is higher than that of ferric carboxymaltose (1000 mg) and considered that listing may result in a rise in the most commonly prescribed dose and the resulting drug cost/patient/course.

Estimated PBS usage & financial implications

- 6.40 This submission was not considered by DUSC.
- 6.41 The submission used a market share approach to estimate the utilisation and financial implications associated with listing ferric derisomaltose.

Table 11: Estimated utilisation and financial implications of recommending ferric derisomaltose to the PBS/RPBS

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Estimated extent of use						
Utilisation of FD						
Estimated financial implications of ferric derisomaltose						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
Estimated financial implications for ferric carboxymaltose						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to PBS/RPBS	\$0	\$0	\$0	\$0	\$0	\$0

Source: Table 4-10, Table 4.11 p81, Table 4-14, Table 4-15 p84, Table 4-16, p83 of the submission

FD = ferric derisomaltose; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits

- 6.42 The submission estimated the overall cost of listing ferric derisomaltose to the PBS/RPBS was likely to be negligible as the market was not expected to change and a cost-minimisation approach was employed. However, there was uncertainty in the estimates as the submission did not include changes in the use of iron sucrose and iron polymaltose, which account for approximately 13% of IV iron dispensing (underestimate).
- 6.43 The PSCR reiterated that ferric derisomaltose is expected to substitute directly for ferric carboxymaltose. As the 2017 DUSC utilisation review confirmed, the low and stable use of iron polymaltose following several years of availability of ferric carboxymaltose and the negligible use of iron sucrose, the listing of ferric derisomaltose is not expected to impact on the use of iron polymaltose or iron sucrose. The ESC agreed with the sponsor that listing ferric derisomaltose on the PBS was unlikely to result in changes to the IV iron market. The ESC considered that the ability to administer ferric derisomaltose at a faster rate and at a higher dose via the IV infusion than ferric carboxymaltose was not likely to expand the IV iron market. The ESC considered that ferric carboxymaltose is usually administered in the general practice setting via an IV injection, rather than an IV infusion, as most general practices lack the resources and equipment required to administer high doses of IV iron via an IV infusion. The ESC considered a similar approach would be expected for ferric derisomaltose.
- 6.44 The PBAC agreed with the sponsor and the ESC that the listing of ferric derisomaltose was not likely to expand the IV iron market in terms of patient numbers beyond that estimated in the submission. However, the PBAC noted that the maximum dose per IV infusion for ferric derisomaltose (1500 mg) is higher than that of ferric carboxymaltose (1000 mg) and considered that listing may result in a rise in the most commonly prescribed dose from the 1000 mg reported in the 2017

DUSC utilisation review. The PBAC considered that this may lead to higher than expected use of ferric derisomaltose and recommended that DUSC undertake a review of utilisation after an appropriate period post listing.

Quality Use of Medicines

- 6.45 The submission did not present any proposals for Quality of Use of Medicine information.

Financial Management – Risk Sharing Arrangements

- 6.46 The submission acknowledged that the main comparator, ferric carboxymaltose, is subject to an SPA and was willing to adopt an equivalent SPA to ensure the cost-minimisation framework was maintained.
- 6.47 The submission and the PSCR also acknowledged that a risk sharing arrangement (RSA) in the form of subsidisation caps is in place for ferric carboxymaltose. The PBAC considered it appropriate for ferric derisomaltose to be included in the same RSA.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended that ferric derisomaltose be listed on the PBS as a Section 85 General Schedule, Unrestricted listing for the treatment of iron deficiency anaemia when treatment with oral iron is ineffective or not tolerated. The PBAC recommended the listing on a cost-minimisation basis with ferric carboxymaltose.
- 7.2 The PBAC considered that the submission's proposed clinical place for ferric derisomaltose, as an alternative IV iron formulation for the treatment of iron deficiency anaemia when treatment with oral iron is ineffective or not tolerated, was appropriate.
- 7.3 The PBAC noted that three IV iron formulations are currently listed on the PBS: iron polymaltose, iron sucrose and ferric carboxymaltose. The PBAC considered that iron polymaltose was not an appropriate comparator due to differences in administration requirements and that iron sucrose was also not appropriate due to differences in administration requirements, dosing and TGA indication. The PBAC accepted ferric carboxymaltose as an appropriate comparator as similarities in administration, dosing and TGA indications meant that it was the IV iron formulation most likely to be replaced by ferric derisomaltose in practice.
- 7.4 The PBAC considered that, although the indirect comparisons presented in the submission meet the non-inferiority margins previously accepted by the PBAC in its consideration of ferric carboxymaltose, there were significant heterogeneity and transitivity issues associated with the trials that made it difficult to draw accurate conclusions regarding the claim of non-inferior efficacy and safety. However, the

PBAC considered that the results of the direct comparison between ferric derisomaltose versus iron sucrose further supported the premise that in equivalent doses, IV iron compounds are likely to lead to comparable efficacy. The PBAC considered that on balance, the claim of non-inferior comparative effectiveness and safety was reasonable.

- 7.5 The PBAC accepted the cost-minimisation analysis presented in the submission and noted that the equi-effective doses were 1 mg ferric derisomaltose: 1 mg ferric carboxymaltose.
- 7.6 The PBAC agreed with the sponsor and the ESC that the listing of ferric derisomaltose was not likely to expand the IV iron market in terms of patient numbers beyond that estimated in the submission. However, the PBAC noted that the maximum dose per IV infusion for ferric derisomaltose (1500 mg) is higher than that of ferric carboxymaltose (1000 mg). The PBAC considered that listing might result in a rise in the most commonly prescribed dose from the 1000 mg reported in the 2017 DUSC utilisation review, as clinicians are likely to use the simplified dosing regimen. The PBAC considered that this might lead to higher than expected use of ferric derisomaltose and recommended that DUSC undertake a review of utilisation after an appropriate period post listing.
- 7.7 The PBAC noted that a RSA in the form of subsidisation caps is in place for ferric carboxymaltose and recommended that ferric derisomaltose be included in the same RSA.
- 7.8 The PBAC noted that the sponsor was willing to adopt an SPA equivalent to that of the main comparator, ferric carboxymaltose, to ensure the cost-minimisation framework was maintained.
- 7.9 The PBAC noted that SPAs are given effect through a deed made under Section 85E of the National Health Act 1953 between the Minister (or his delegate) and the responsible person. The PBAC further noted that the Minister (or his delegate) has requested advice under section 101(3) of the Act as to whether ferric derisomaltose meets criteria 1 and 2 of the SPA criteria when used for the treatment of iron deficiency anaemia when treatment with oral iron is ineffective or not tolerated.
- 7.10 The PBAC advised the Minister that, in its view, ferric derisomaltose meets criterion 1 but not the first component of criterion 2 for an SPA.

- Criterion 1: The medicine treats a significant medical condition, and the Pharmaceutical Benefits Advisory Committee (PBAC) advises that it generates substantial incremental benefit for the intended patient population.

The PBAC considered that Criterion 1 appears to be met when considering ferric derisomaltose in comparison to placebo. Ferric derisomaltose is used to treat iron deficiency anaemia when treatment with oral iron is ineffective or not tolerated and generates a benefit for people with this condition.

- Criterion 2: The PBAC advises that the medicine has unique characteristics compared to any available alternative therapies or the medicine is recommended for listing in comparison with a medicine that has a similar arrangement.

The PBAC considered that the first part of criterion 2 was not met. Based on the evidence presented, the PBAC considered that ferric derisomaltose has not been shown to have unique characteristics compared to ferric carboxymaltose. However, the PBAC did recommend listing in comparison to ferric carboxymaltose that has a current Special Pricing Arrangement.

- 7.11 The PBAC recommended that ferric derisomaltose should not be treated as interchangeable with any other drugs.
- 7.12 The PBAC advised that ferric derisomaltose is suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that the Early Supply Rule should not apply.
- 7.14 The PBAC noted that this submission was not eligible for Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
IRON Iron (as ferric derisomaltose) 500 mg/5 mL injection, 1 x 5 mL vial	2	1	Monofer®	Pfizer Australia

9 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.

10 Sponsor's Comment

The sponsor had no comment.