6.01 DEFERASIROX, 125 mg dispersible tablet, 28, 250 mg dispersible tablet, 28, 500 mg dispersible tablet, 28, Exjade®, Novartis Pharmaceuticals Pty Ltd

1 Purpose of Application

1.1 Section 100 listing for deferasirox (DFX) for treatment of iron overload associated with transfusion dependent malignant disorder of erythropoiesis and non-transfusion dependent thalassaemia.

2 Requested listing

2.1 Two alternative listings (achieving the same coverage) were proposed:

1) maintain the existing PBS listing (i.e., prior to the November 2014 PBAC recommendation) so both malignant and non-malignant conditions of erythropoiesis are included under one listing; OR
2) amend the listing so that there would be separate listings for a) non-malignant conditions and b) transfusion-dependent malignant conditions of erythropoiesis requiring iron chelation therapy (ICT).

2.2 The submission requested identical published prices for DFX compared to the current listing, but is offering a higher rebate of [redacted]% off the ex-manufacturer price (an increase from the current [redacted]% rebate) in patients with transfusion dependent malignant conditions and non-transfusion dependent thalassemia (NTDT).

2.3 Suggestions and additions proposed by the Secretariat were addressed in the PSCR and the revised requested listings are presented below.

Non-malignant disorders restriction: Public

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty -Public Published (effective)	Proprietary Name and Manufacturer
DEFERASIROX				
125 mg tablet: dispersible, 28	6	5	$1401.48 ($[redacted])	Exjade® NV
250 mg tablet: dispersible, 28	6	5	$2802.90 ($[redacted])	
500 mg tablet: dispersible, 28	6	5	$5605.80 ($[redacted])	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload

Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must not have a malignant disease

Non-malignant disorders restriction: Private

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty (effective)	Proprietary Name and Manufacturer
DEFERASIROX				
125 mg tablet: dispersible, 28	6	5	$1448.26 ($[redacted])	Exjade® NV
250 mg tablet: dispersible, 28	6	5	$2849.68 ($[redacted])	
500 mg tablet: dispersible, 28	6	5	$5652.58 ($[redacted])	

Category / Program	Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must not have a malignant disease

Malignant disorders restriction: Public and Private (Initial)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty -Public Published (effective)	Dispensed Price for Max. Qty - Private Published (effective)	Proprietary Name and Manufacturer
DEFERASIROX					
125 mg tablet: dispersible, 28	6	2	$1401.48 ($[redacted])	$1448.26 ($[redacted])	Exjade® NV
250 mg tablet: dispersible, 28	6	2	$2802.90 ($[redacted])	$2849.68 ($[redacted])	
500 mg tablet: dispersible, 28	6	2	$5605.80 ($[redacted])	$5652.58 ($[redacted])	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload

PBS Indication:	Chronic iron overload
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must be red blood cell transfusion dependent. AND Patient must have received at least 20 units of red blood cell transfusion prior to commencing therapy. AND Patient must have a serum ferritin level of greater than 1000 microgram/L. AND Patient must have an underlying malignant disease with a prognosis of 1 year or greater that is scored as low or intermediate-1 risk according to the International Prognostic Scoring System (IPSS).
Administrative Advice	A patient is considered to have an underlying disease with a prognosis of 1 year or greater year if they do not possess any life shortening co-morbidities.

Malignant disorders restriction: Public and Private (Continuing)

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty -Public Published (effective)	Dispensed Price for Max. Qty - Private Published (effective)	Proprietary Name and Manufacturer
DEFERASIROX					
125 mg tablet: dispersible, 28	6	2	$1401.48 ($[redacted])	$1448.26 ($[redacted])	Exjade® NV
250 mg tablet: dispersible, 28	6	2	$2802.90 ($[redacted])	$2849.68 ($[redacted])	
500 mg tablet: dispersible, 28	6	2	$5605.80 ($[redacted])	$5652.58 ($[redacted])	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload
Treatment phase:	Continuing

Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised therapy with this drug for this condition. AND Patient must have a blast percentage of less than 20% in bone marrow or peripheral blood.
Administrative Advice	Interruption of treatment should be considered if serum ferritin levels fall consistently below 500 microgram/ml.

2.4 The requested listing covering myelodysplastic syndrome (MDS) was based on a claim of superior efficacy and similar safety compared to basic supportive care without ICT. However, no randomised controlled trials or sufficiently adjusted observational data were presented to support this claim. The listing covering NTDT was based on a claim of superior effectiveness relative to placebo, although no economic evidence was presented for DFX for this indication.

2.5 The ESC noted that DFX is a highly specialised drug, which makes administration outside an institutional environment problematic; the ESC also agreed that the patient target group was clearly identifiable. In considering this, the ESC accepted that the request for a S100 (Highly Specialised Drugs) listing was appropriate.

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

3 Background

3.1 DFX was TGA registered on 6 July 2006 for the treatment of chronic iron overload:
- due to blood transfusions (transfusional haemosiderosis) in adults and paediatric patients 6 years and older;
- in paediatric patients aged 2 to 5 years who are unable to take desferrioxamine (DFO) therapy or in whom DFO has proven ineffective.

3.2 At the ACPM 294th meeting in October 2013 it was additionally approved for treatment of chronic iron overload in patients with NTDT syndromes aged 10 years and older (i.e. new indication since DFX PBS listing in 2006).

3.3 DFX was PBS listed in 2006 for the indication of "chronic iron overload in patients with disorders of erythropoiesis". At the November 2014 meeting, the PBAC reflected upon the higher than expected utilisations and the ages of initiating patients revealed by the DUSC review, and considered it was apparent that most use was now outside the transfusion-dependent thalassemia population where DFX was shown to be cost effective. Further, it seemed highly likely that most use was now in patients with MDS where no data for cost effectiveness had been considered by the PBAC. The PBAC therefore recommended the PBS listing of DFX be restricted to

"chronic iron overload in patients with transfusion dependent non-malignant disorders of erythropoiesis", until it received an evidence-based application to include other clinical indications. This would re-align Australian Government funding with the previously considered clinical and cost effectiveness evidence. In doing so, the PBAC encouraged a new application, as this recommendation, if implemented, would mean that some patients currently being prescribed PBS-subsidised DFX would no longer be able to access DFX on the PBS.

3.4 The ESC noted the submission's assumption that the requested revision was to apply equally to DFX and DFO (and that such a revision could leave MDS and NTDT patients with no access to subsidised ICT), but understood it was not PBAC's intention to apply the requested revision to DFO.

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

4 Clinical place for the proposed therapy

4.1 DFX is an oral treatment for patients with iron overload, which can occur as a consequence of frequent red blood cell (RBC) transfusions required to manage a range of disorders of erythropoiesis, such as β thalassaemia and MDS (a disorder where immature blood cells fail to develop normally). Iron overload can also occur in transfusion independent patients where accumulation of iron is due to increased absorption. Excess body iron is thought to deposit in organs such as the liver and heart (in β thalassemia patients who begin transfusions at birth, this is observed at around 10 years of age on average). iron overload and the improvement in survival with ICT have been unequivocally demonstrated in transfusion dependent β thalassaemia, but the consequences of iron overload and the benefits of ICT are less well understood in MDS or NTDT. However, it appeared ICT in MDS was gaining traction due to publication of large observational studies showing a potential benefit.

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

5 Comparator

5.1 The submission nominated best supportive care without ICT as the main comparator. This was mainly based on the assumption that the PBAC recommendation for DFX in November 2014 would apply equally to DFO, thus no chelating agents would be available on the PBS for patients with MDS. However, this was not appropriate given the PBAC recommendation was limited to DFX. The ESC considered that while substitution to DFO could not be ruled out, a comparison versus placebo remained informative; utilisation data indicate that DFO's utilisation on PBS was low and declining and, more importantly, the cost effectiveness of DFO in MDS was unknown.

5.2 For the specific requested listing for patients with NTDT, supporting data from the THALASSA trial was provided subsequent to the main submission as an additional appendix. No comparator was nominated by the submission for NTDT. The THALASSA trial investigated the efficacy of DFX in NTDT compared with placebo. The submission contended the usage of DFX in this population was likely to be low (5% of total DFX usage) and a listing would ensure continuity of care.

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 and welcomed the input from individuals (3), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with deferasirox, including improvement in quality of life once the iron overload is reduced, and a reduction in both the patient's requirement for transfusion and the risk of complications of transfusional iron overload. It was considered that deferasirox would be unaffordable to patients if not PBS-subsidised.

6.3 The PBAC noted the advice received from the Haematological Society of Australia and New Zealand (HSANZ) and the Thalassaemia Society of NSW clarifying the likely use of deferasirox for NTDT patients in clinical practice. The PBAC specifically noted the advice that the use of deferasirox was very important in the treatment of patients with NTDT who are at significant risk of iron overload. NTDT patients can suffer iron overload even though not regularly transfused, with iron deposition predominantly in the liver (causing liver fibrosis and cirrhosis, associated with the risk of hepatocellular carcinoma) and endocrine glands (leading to a variety of endocrine disturbances e.g. hypothyroidism and hypogonadism). HSANZ and the Thalassaemia Society of NSW also considered any change from a once a day oral regime (DFX) to a subcutaneous infusion regime (DFO) was likely to cause a marked reduction in compliance. The availability of DFX on the PBS would also lessen the financial strain on the families involved. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.4 The PBAC noted the advice received from the Leukaemia Foundation which conducted a short consumer comments survey for people affected by MDS. The respondents noted the impacts of iron overload include organ failure (30%), heart problems (25%) and iron deposits anywhere in the body (20%). Only approximately three in ten of the MDS patients surveyed required iron chelation and were currently on DFX. It was also noted access to deferasirox on the PBS reduced the financial strain to patients and carers. The Leukaemia Foundation suggested that given the elderly demographic, many people would not have the option of undergoing a bone marrow transplant and thus blood product support may be the mainstay of treatment or supportive therapy during chemotherapy treatment, of which they are on indefinitely. The PBAC noted this advice and considered the requirement for iron chelation for MDS patients varied depending on their prognosis.

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

Clinical trials

6.5 The submission's literature search focused on identifying evidence of ICT in MDS. It was argued this was to be the focus of the submission as it was the major driver behind the PBAC recommendation in November 2014.

6.6 No randomised controlled trials reporting survival outcomes were identified for any iron chelator (i.e., DFX, DFO or deferiprone (DFP)) in the MDS population. The submission was based on eight non-randomised studies (two prospective (Lyons publications and Rose 2010), and six retrospective (Delforge 2014, Neukirchen 2012, Raptis 2010, Remacha 2014, Leitch 2008 and Komrokji 2011; although Delforge 2014 has elements of a prospective design). These 8 studies were nominated by the submission as the current best available evidence for estimating the survival effect of ICT on MDS patients. Two published meta-analyses comparing ICT with no ICT were also identified in the submission's literature search (Mainous 2014 and Meerpohl 2014), but as the meta-analyses do not include additional relevant studies, they were not included as primary evidence to the submission.

6.7 In addition to the published literature, the submission presented analyses of individual patient data (IPD) from the MORE registry (a predominately prospective observational study with approximately 5 years of follow up), as well as a 10% PBS sample. Although the 8 non-randomised studies were flagged as the best available evidence, the results of the sponsor's in-house analyses of IPD and the 10% PBS sample were used in the modelled economic evaluation. The submission argued this was appropriate as the PBS data set was more reflective of survival of MDS patients using DFX in an Australian setting (assuming that over 55 year olds using DFX had MDS) and the MORE registry was currently the largest (599 subjects), recent prospective study with the longest follow-up (four to five years). The sponsor further argued that the IPD analysis allowed some adjustment to be made for uncertainty introduced by the non-randomised design. This consisted of adjusting treatment effect for available confounders of survival including age, sex, transfusions (expressed as total RBC units), number of comorbidities, ECOG and IPSS risk category.

6.8 Details of the studies presented in the submission are provided in Table 1.

Table 1: Non randomised studies and associated reports presented in the submission

Studies	Reports	Comment
Lyons	Lyons, R. M., Marek, B. J., Paley, C., Esposito, J., Garbo, L., DiBella, N., et al. (2014). "Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry." Leukemia Research 38(2): 149-154. Lyons et al 2014.	Paper 24 month follow up
	Lyons, R.M., Marek, B.J., Paley, C., Esposito, J., Garbo, L., DiBella, N. & Garcia-Manero, G. (2012) Relationship between chelation and clinical outcomes in 600 lower-risk MDS patients: registry analysis at 36 months. Blood (ASH Annual Meeting Abstracts), 120, 3800. Lyons et al 2013.	Abstract 36 month follow up
	Lyons, R. M., Marek, B. J., Paley, C. S., Esposito, J., McNamara, K., Garbo, L., et al. (2013). "48-Month update on survival and AML transformation in a 600-patient registry of lower-risk MDS patients." Blood 122(21). Lyons et al 2013	Abstract 48 month follow up
	Lyons, R.M., Marek, B.J., Paley, C., Esposito, J., McNamara, K., Garbo, L., DiBella, N. & Garcia-Manero, G. (2015). Relationship Between Chelation and Clinical Outcomes in Lower-Risk Patients with Myelodysplastic Syndrome (MDS):	Abstract 60 month follow up

Studies	Reports	Comment
	Registry Analysis at 5 Years. Accessed February 2015	
	MORE registry individual patient data	Unpublished and committee-in-confidence
	Additional publications	
	Lyons, R. M., B. J. Marek, et al. (2011). "24-month analysis of the impact of chelation on clinical outcomes in a 600 patient registry of lower-risk MDS patients." Blood 118(21). Lyons et al 2011	-
	Lyons, R. M., B. J. Marek, et al. (2013). "A 36-month analysis of treatment patterns and outcomes in patients with lower-risk myelodysplastic syndromes from a prospective observational study." Journal of Clinical Oncology 31(15). Lyons et al 2013.	-
	Garcia-Manero, G., B. J. Marek, et al. (2009). "Clinical parameters in 391 iron-overloaded patients with lower-risk MDS enrolled in a prospective, non-interventional multicenter registry." Blood 114(22). Garcia-Manero et al 2013	-
Rose 2010	Rose, C., Brechignac, S., Vassilief, D., Pascal, L., Stamatoullas, A., Guerci, A., Larbaa, D., Dreyfus, F. & Beyne-Rauzy, O., Chaury MP, Roy L, Cheze S, Morel P, Fenaux P; GFM (Groupe Francophone des Myelodysplasies) (2010) Does iron chelation therapy improve survival in regularly transfused lower risk MDS patients? A multicenter study by the GFM. Leukemia Research, 34, 864–870. Rose et al 2010.	Paper
Delforge 2014	Delforge, M., Selleslag, D., Beguin, Y., Triffet, A., Mineur, P., Theunissen, K., Graux, C., Trullemans, F., Boulet, D., Van Eygen, K., Noens, L., Van Steenweghen, S., Lemmens, J., Pierre, P., D'hondt, R., Ferrant, A., Deeren, D., Van De Velde, A., Wynendaele, W., Andre, M., De Bock, R., Efira, A., Breems, D., Deweweire, A., Geldhof, K., Pluymers, W., Harrington, A., MacDonald, K., Abraham, I. & Ravoet, C. (2014) Adequate iron chelation therapy for at least six months improves survival in transfusion-dependent patients with lower risk myelodysplastic syndromes. Leukemia Research, 38, 557–563. Delforge et al 2014.	Paper
Neukirchen 2012	Neukirchen, J., Fox, F., Kundgen, A., Nachtkamp, K., Strupp, C., Haas, R., Germing, U. & Gattermann, N. (2012) Improved survival in MDS patients receiving iron chelation therapy - a matched pair analysis of 188 patients from the Dusseldorf MDS registry. Leukemia Research. 36, 1067–1070. Neukirchen et al 2012.	Paper
	Additional publications	
	Fox, F., Kundgen, A., Nachtkamp, K., Strupp, C., Haas, R., Germing, U., et al. (2009). "Matched-pair analysis of 186 MDS patients receiving iron chelation therapy or transfusion therapy only." Blood 114(22). Fox et al 2009.	Abstract
Raptis 2010	Raptis, A., Duh, M.S., Wang, S.T., Dial, E., Fanourgiakis, I., Fortner, B., Paley, C., Mody-Patel, N., Corral, M. & Scott, J. (2010) Treatment of transfusional iron overload in patients with myelodysplastic syndrome or severe anemia: data from multicenter clinical practices. Transfusion, 50, 190–199. Raptis et al 2010.	Paper
	Additional publications	
	Raptis, A., M. S. Duh, et al. (2009). "Treatment of transfusional iron overload in patients with myelodysplastic syndrome or severe anemia: Data from multi-center clinical practices." Value in Health 12(3): A132. Raptis et al 2009.	Abstract
Ramacha 2014	Leitch, H.A., Leger, C.A., Goodman, T.A., Wong, K.K., Wong, D.H.C., Ramadan, K.M., Rollins, M.D., Barnett, M.J., Galbraith, P.F. & Vickars, L.M. (2008) Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. Clinical Leukemia, 2, 205–211. Letch et al 2008.	Paper
	Additional publications	
	Leitch, H. A., Chan, C., Leger, C. S., Foltz, L. M., Ramadan, K. M. and Vickars, L.	-

Studies	Reports	Comment
	M. (2011). "Improved survival with iron chelation therapy for lower IPSS risk MDS appears to have a stronger association in patients with a non-RARS diagnosis." Blood 118(21). Letch et al 2011.	
	Leitch, H. A., Chan, C., Leger, C. S., Foltz, L. M., Ramadan, K. M. and Vickars, L. M. (2012). "Improved survival with iron chelation therapy for red blood cell transfusion dependent lower IPSS risk MDS may be more significant in patients with a non-RARS diagnosis." Leukemia Research 36(11): 1380-1386. Letch et al 2012.	-
Letich 2008	Remacha, A. F., B. Arrizabalaga, A. Villegas, M. S. Duran, L. Hermosin, P. R. De, M. Garcia, M. D. Campelo, G. Sanz and O. B. O. T. Iron- (2014). "Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications." Annals of Hematology. Ramacha et al 2014	Paper
	Remacha, A., Arrizabalaga, B., Villegas, A., Duran, M.S., Hermosin, L., de Paz, R., Garcia, M., Garcia, R., del Canizo, C., Sanz, S. & Sanz, G. (2012) The IRON2 Study. A retrospective observational study to describe the evolution of iron overload in patients with low-risk myelodysplastic syndrome. Blood, 120, 1723. Ramacha et al 2012.	Abstract
Komrokji 2011	Komrokji, R.S., Al Ali NH, Padron E, Lancet JE, List AF (2011) Impact of iron chelation therapy on overall survival and AML transformation in lower risk MDS patients treated at the moffitt cancer center. Blood, 118, 1196–1197. Komrokji et al 2011.	Abstract
Mainous 2014	Mainous, A. G., R. J. Tanner, et al. (2014). "The impact of chelation therapy on survival in transfusional iron overload: A meta-analysis of myelodysplastic syndrome." British Journal of Haematology. Mainous et al 2014.	-
Meerpohl 2014	Meerpohl, J. J., L. K. Schell, G. Rücker, N. Fleeman, E. Motschall, C. M. Niemeyer and D. Bassler (2014). "Deferasirox for managing iron overload in people with myelodysplastic syndrome." Cochrane Database of Systematic Reviews. Meerpohl et al 2014.	-

Source: Table B.2-2, pp52-54 of the submission

6.9 The key features of non-randomised studies are summarised in Table 2.

Table 2: Key features of the included evidence of ICT (with any agent) versus no ICT in MDS

Study	N*	Design/ data collection period/ median follow up/country	Risk of bias	Patient population/definition of chelation therapy	Outcome(s)	Used in model ?
Prospective non randomised studies						
Lyons 2014	600 (No-ICT:337 ICT: 263 ICT>6mth: 191)	OL, O, P, MC Enrolled 2008 24 mths interim analysis *USA (118 centres)*	High	Age ≥18 years, Lower risk MDS# by IPSS, WHO and/or FAB criteria, tIO, SF ≥1000 ng/mL, ≥20 PRBC units, or ongoing transfusion requirement of ≥6 units every 12 weeks	OS (from diagnosis) Progression to AML	No
IPD from MORE registry	599 (No-ICT:239 ICT: 271 ICT>6mth: 202)	OL, O, P, MC Enrolled 2008 48-60 mths *USA (118 Centres)*	High		OS (from diagnosis) Progression to AML	Yes
Rose 2010	97^ (No ICT: 44 ICT>6mth: 53 (48 were initiated prior to study enrolment)	OL, O, P, MC Enrolled May-June 2005 30mths *France (18 centres)*	High	MDS low or int1 IPSS; Patients received RBC transfusions. chelation defined as weak or adequate+	OS (from diagnosis)	No
Retrospective non randomised studies						
Delforge 2014	127 (No-ICT:47	RS, MC, chart review (Oct 2010-Mar 2011 to	High	MDS low or int1 IPSS. Treated with DFO or DFX,	OS (from diagnosis)	No

Study	N*	Design/ data collection period/ median follow up/country	Risk of bias	Patient population/definition of chelation therapy	Outcome(s)	Used in model ?
	ICT≤6mth: 18 ICT>6mth: 62)	identify subjects) and reported events in the 2 yrs prior, i.e. 2008-2011) 25.4mth *Belgium (28 centres)*		weak and adequate chelation.		
Neukirchen 2012	188 (No ICT: 94 Matched patients ICT: 94)	RS, MC, chart review for patients taking ICT, matched to those not taking ICT using age at dx, MDS type and IPSS score (all Dx 1975-2008) 0.5-27 yrs^ *Germany (Dusseldorf MDS registry)*	High	MDS – risk level not specified; IO (SF ≥1000 μg/L, or a history of multiple transfusions and SF ≥500) μg/L; receiving long term chelation therapy	OS (assumed from diagnosis)	No
Raptis 2010	128 (ICT eligible) 78 (ICT eligible with lower risk MDS#) No ICT: 46 ICT: 32	RS, MC, chart review (Dx 1998-2007) ICT: 55.2 (4.6yrs) NO ICT: 32.4 (2.7yrs) *USA (US P4 healthcare network)*	High	Age ≥21 years; MDS (93.5%), aplastic anaemia or other severe anaemia, ≥1 RBC transfusion; Subgroup with lower risk MDS#; Eligibility criteria for ICT: ≥2 SF 1000 μg/L or ≥20 units of RBCs transfused >1 prescription DFX or ≥1 dose of sc DFO Matching: age at dx (±5 years), gender, not for comorbidities and intensity of transfusion during the course of the disease.	OS (from diagnosis)	No
Remacha 2014	263 No ICT:116 ICT: 147 ICT≥6mth: 96	RS, MC, chart review (Mar 2010-Mar 2011) 41 mths (IQR:19-80) *Spain (47 hospitals)*	High	Age ≥18 yrs; lower risk MDS: Low/Int-1 IPSS or Spanish prognostic index 0-1; transfusion dependent; ≥10 RBC transfusions during last 12 months prior to study entry.	OS (assumed from diagnosis)	No
Leitch 2008	ICT: 36 No ICT (matched control):18 ICT: 18	RS, MC, chart review (patients seen between 1981-2006) 51.1mths *Canada (St Pauls, Vancouver)*	High	MDS; Low/Int-1 IPSS Criteria for initiating ICT: ≥1 of the following: SF >2000 μg/L, transfusion of ≥20 units of RBCs, or clinical evidence of iron overload.	OS (from diagnosis)	No
Komrokji 2011(abst)	97 No ICT: 52 ICT: 45	RS, MC, chart review (patients seen between July2001-July 2009) 85.7 mths from diagnosis *USA (Moffat Cancer centre)*	High	MDS: Low/int-1 IPSS; SF≥1000 μg/L	OS (from diagnosis)	No

Study	N*	Design/ data collection period/ median follow up/country	Risk of bias	Patient population/definition of chelation therapy	Outcome(s)	Used in model ?
Meta-analyses						
Mainous 2014	1562	The meta-analysis pooled the observed differences in OS from the included Lyons 2014 Remacha 2014; Leitch 2008; Komrokji 2011; Delforge 2014; Neukirchen 2012; Raptis 2010 and Rose 2010 publications				No
Meerpohl 2014	0	The Cochrane meta-analysis looked for trials of DFX versus placebo or other ICTs in MDS irrespective of the trial's outcome measures. Although the literature search identified 3 ongoing and 1 completed trials, no data from any of these RCTs were available for inclusion in the review. Apart from TELESTO (still ongoing), the other identified trials do not report survival outcomes.				No

Abbreviations: Dx, diagnosis; IPSS, International Prognostic Scoring System; Int-1, intermediate-1; ICT, iron chelation therapy; LE, life expectancy; MDS, myelodysplastic syndrome; NR, not reported; PRBC, packed red blood cell; RBC, red blood cell; sc, subcutaneous; SF, serum ferritin; tIO; transfusional iron overload; IO=iron overload; MC=multi-centre; O=observational, OL = open label; OS=overall survival; P = prospective; RS=retrospective; ICT=iron chelation therapy, MDS=myelodysplastic syndrome; Dx=diagnosed; IQR=interquartile range; abst=abstract

* number of patients analysed

^ registry was established in 1982, patients diagnosed between 1975 and 2008, so follow up estimated between 0.5-27 yrs

+ Adequate chelation is defined as: DFO 40mg/kg/day in slow infusion over 8-12 hrs, for at least 3 days per week, DFX (20-30mg/kg/day) or DFP (3-75mg/kg/d), weak chelation is defined as DFO <3g/week (either IV once after each RBC transfusion or as SC bolus injection.

lower risk MDS defined by either: IPSS: low or intermediate-1; WHO: RA, RARS, RCMD, RCMD-RS, or 5q or FAB: RA, RARS and RA with excessive blasts (<11%) for Lyons et al only.

Source: compiled during the evaluation

6.10 The THALASSA trial was the only randomised trial of DFX in NTDT identified. The THALASSA trial was a prospective, double blind, placebo controlled phase II trial that compared two doses of DFX (5mg/kg/day and 10mg/kg/day) versus placebo over a one year period in 166 subjects with NTDT.

6.11 Details of the trial and associated reports presented in the addendum are provided in Table 3.

Table 3: Randomised study and associated reports presented in the addendum to the submission

Trials	Reports	Comment
THALASSA	Taher, A. T., et al. (2012). "Deferasirox reduces iron overload significantly in nontransfusion-dependent thalassemia: 1-Year results from a prospective, randomized, double-blind, placebo-controlled study." Blood 120(5): 970-977.	-
	Taher, A. T., et al. (2012). "Deferasirox continues to reduce iron overload in non-transfusion-dependent thalassemia: A one-year, open-label extension to a one-year, randomized, double-blind, placebo-controlled study (thalassa)." Blood 120(21).	-

Source: Table B.2.3, pp11-12 of the section B addenda for NTDT.

6.12 The key features of the THALASSA trial are summarised in Table 4.

Table 4: Key features of the THALASSA trial (DFX in NTDT):

Study	N	Design/Duration	Risk of bias	Patient population	Outcome	Used in model
THALASSA	166	R, DB, 12 mths	low	Male or female aged ≥10 years with NTDT, no	change in LIC from	No

		OL extension study up to 24 mths		transfusion within 6 mths prior to enrolment. LIC ≥5 mg Fe/g dry liver weight (measured by MRI). SF > 300ng/ml	baseline at wk 52.	

Abbreviations: DB = double blind; OL = open label; R=randomised; LIC = liver iron concentration; mth = month; wk = week; SF = serum ferritin
Source: compiled during the evaluation

Comparative effectiveness

6.13 The observational studies in MDS reported that ICT was associated with longer median OS compared to no ICT. Results are summarised in Table 5 below. The differences ranged between 25 months (2 years) to more than 185 months (15 years). Most studies found a difference in the region of 50 months (6 years).The ESC questioned whether this was plausible given the likely advanced age of MDS patients and the fact that they are transfusion dependent. The ESC also considered that the amount of survival attributable to DFX in the studies was highly uncertain.

Table 5: Overall Survival in the non-randomised studies (bold typography indicates significant differences in median survival between ICT and no ICT groups)

Study Follow up (mths) Population	Overall Survival Median months (IQR) Unadjusted			Adjusted HR (ICT versus no ICT)	
	No ICT	ICT (P value vs no ICT)	ICT ≥6 mths (P-value vs no ICT)	Variables adjusted	HR (95%CI)^ p-value
PROSPECTIVE					
Lyons 2014 24 months - -All	N=337 52.2 (24.0, 136.2)	N= 263 **99.3 (54.1, NA) P<0.0001**	N = 191 **104.4 (63.4, NA) P<0.0001**	NR	NR
- -IPSS 0 group	N=56 53.6 (4.1, 66.3)	n=56 NR	N=38 **98.7(12.8, 103.8) P=0.028**		
- -IPSS Int-1 group	N=110 44.7 (5.5, 151.6)	N=71 NR	N=57 **70.0 (12.5, 83.4) P=0.013**		
Lyons 2012 (abst) 36 months	N=336 50.0 (1.8-289.4)	N= 264 96.8 (2.3-187.8)	N = 200 **102.1 (2.3-187.8) P=0.0001**	NR	NR
Lyons 2013 (abst) 48 months - -All	N=330 48.7 (1.8-289.4)	N= 269 96.8 (2.3–187.8)	N = 202 **102.5 (2.3–187.8) P<0.0001**	NR	NR
Lyons 2014 (abst) 60 months - All	N=328 47.8 (43.4, 53.1)	N= 271 **88.0(78.4, 103.0) P<0.0001**	N = 202 **100.0 (83.4, 118.2) P<0.0001**	NR	NR
- No CVC	n=42 34.0	n=72 **69.3 (P<0.0001)**	n=60 **79.3 (P<0.0001)**		
- With CVC	n=286 43.4	n=199 67.7	n=142 72.6		
- No endocrine co-morbidity	n=162 38.5	n=149 **67.1 (P<0.0001)**	n=114 **69.6 (P<0.0001)**		
- With endocrine co-morbidity	n=166 44.6	n=122 75.0	n=88 81.8		
Rose 2010 30 months (2.5 years) -All	n=44 53	- -	n=53 **124 (P<0.0003)**	Age, IPSS, transfusion requirement	**0.302 (0.16, 0.58) P=0.0003**
- Adequate versus	n=12	-	n=41		

Study Follow up (mths) Population	Overall Survival Median months (IQR) Unadjusted			Adjusted HR (ICT versus no ICT)	
	No ICT	ICT (P value vs no ICT)	ICT ≥6 mths (P-value vs no ICT)	Variables adjusted	HR (95%CI)^ p-value
weak chelation	Weak chelation 85	-	Adequate chelation **124 (P<0.001)**		
- IPSS low	n=15 70	- -	n=30 **138 (P=0.015)**		
- IPSS int 1	n=29 36	 -	n=23 **115 (P=0.0003)**		
- <3 PRBC-mth	n=NR 77	 -	n=NR **124 (P=0.03)**		
- - ≥3 PRBC-mth	n=NR 28	- -	n=NR **138** (P=0.0001)		
- -Aged < 77 years	n=NR 36	- 	n=NR **Not reached P=0.0001**		
- -Aged ≥77 years	n=NR 77	 -	n=NR **124 (P=0.04)**		
RETROSPECTIVE					
Delforge 2014 24 months -All	n = 47 37.2 (SE 4.8)	n = 80 **122.4 (SE 16.8) P<0.001**	n = 62 **126 (SE 26.4) P<0.001**	Age, gender	**0.22 (0.12, 0.41) P<0.001** (ICT ≥6mth)
- Adequately chelated patients	n =47 37.2 (SE: 4.8)	n=56/80(70%) **126 (SE:24) P<0.001***	-	Age, gender	**0.22 (0.12, 0.41) P<0.001** (adequate chelation)
- Weakly chelation	n=47 37.2 (SE: 4.8)	n=24/80(30%) **51.6 (SE 0.8) ***	- -	NR	NR
Neukirchen 2012 NR - -All	49	**75 (P=0.002)**	-	NR	NR
- -Higher risk MDS	NR	NR	-		
- -Lower risk MDS	NR	**NR (P=0.008)**	-		
Raptis 2010 ICT: 55.2 (4.6 yrs) No ICT:32.4 (2.7yrs) - -ICT-eligible patients all MDS risk levels (N = 128)	n=74 56.4	n=54 **104.4 (P=0.02)**	- -	Age at MDS/severe anaemia diagnosis, gender, total units of RBC transfused, and MDS risk level at becoming ICT-eligible (lower-risk vs. higher-risk vs. unclassified or other)	**0.372 P=0.03**
- -ICT-eligible patients MDS low risk (N = 78)	70.8	112.8 (P=0.12)	-		
Remacha 2014 41 months - All	n = 116 153 (95%CI:78 - 228)	n = 146 Not reached	- -	Age, IPSS	**0.361 (0.159, 0.822) P<0.015**
Remacha 2012 (abs) Duration of FU: NR n=228	n=NR 105	N=NR 133 (P=0.009)		NR	**NR**
Leitch 2008 51.1 months - All	n = 18 40.5	n = 18 **>226 (P=0.003)**	- -	Matched controls with similar clinical features	**0.29 (0.10, 0.79) P=0.01**
Komrokji 2011 85.7 months from Dx - All	n = 52 33.7 (38-80)[b]	n = 45 **59 (22-48)** [b] **P=0.013**	- -	Age, cytogenetics	**0.52 (0.31, 0.87) P=0.013.**

Abbreviations: MDS, myelodysplastic syndrome; NR=Not reported; OS, overall survival; PRBC, packed red blood cell; RBC, red blood cell; SE=standard error; IQR=interquartile range, Dx=diagnosis; FU=follow up

[a] Calculated for the submission.

[b] as reported within the abstract.

* results were also statistically significantly different between adequately chelated patients (30%) relative to those chelated weakly (63%) (p = 0.001).

^ a HR lower than 1 favours ICT as it indicates a lower risk of death at any time compared to no ICT.

Source: Table Lyons (2014); Neukirchin (2012); Raptis (2012); Rose (2010); Delforge et al (2014) Fig 2'4; Letch (2008) pp207-208; Remacha (2014) page nr; Remacha (2012) Table 1; Komrokji (2011).

6.14 When interpreting the results the evaluator considered it important to note that there were differences across the observational studies with regards to baseline prognostic factors such as age, MDS risk status and iron status. There were also differences in how RBC dose was reported and the frequency of reporting between arms (e.g. less frequent serum ferritin level monitoring in non-chelated patients in Rose 2010). The studies were also likely confounded by clinicians potentially selecting patients with better anticipated prognosis for treatment with ICT and the fact that there were notable differences between the ICT versus no ICT groups within studies; particularly with respect to the greater use of azacitidine, lenalidomide and thalidomide in the ICT groups of Lyon 2014 and Rose 2010 studies, respectively, compared with the no ICT groups.

6.15 The ESC noted that a subset of the reported studies attempted to adjust for systematic differences in key baseline prognostic factors by presenting both univariate and multivariate Cox models for OS. However, as different sets of adjusting covariates were used in each study, it remained difficult to directly compare the adjusted treatment effect from any one study against another. The ESC considered this multivariate approach did not correct the adjusted Hazard Ratios (HR) for known or potential confounders, either not included in the model or not collected. Furthermore, no estimate was provided around the minimum effect size required for an unobserved confounder to significantly change the inference of an OS advantage attributable to ICT (for example, via a Rosenbaum sensitivity analysis). The Pre-PBAC response (p 2) conducted these additional analyses using data from the MORE registry and neither analysis demonstrated major inconsistencies with the multivariate adjustment approach adopted in the base case.

6.16 The ESC agreed that the magnitude of the effect of ICT on OS in MDS could only be established in a prospective RCT; one such trial of DFX versus placebo was underway (results were not expected until 2018).

6.17 The ESC noted the submission's assertion that MDS patients undergoing ICT may be less likely to progress to acute myeloid leukaemia (AML), however considered that this assertion was not causatively supported by the evidence provided.

6.18 With regards to the comparative effectiveness of DFX in NTDT the ESC noted the results of the THALASSA trial, whereby there was a significant reduction in the change in liver iron concentration at 52 week follow up. See Table 6 below.

Table 6: Repeated measurements analysis of variance of absolute change in serum ferritin between baseline and fourth quarter

	Deferasirox		Placebo
	5 mg/kg/day (N=55)	10 mg/kg/day (N=55)	(N=56)
Change from baseline			
N	55	55	56
Least squares mean	-120.69	-222.00	114.54
95% confidence interval	-203.15, -38.24	-304.46, -139.54	32.83, 196.26
Difference deferasirox – Placebo			
Least squares mean	**-235.24**	**-336.54**	-
95% confidence interval (1)	**-365.99, -104.49**	**-467.29, -205.79**	-
p-value (2)	**<.001**	**<.001**	-
Difference deferasirox 10 mg/kg/day - deferasirox 5mg/kg/day			
Least squares mean	-	-101.31	-
Standard error	-	59.056	-
95% confidence interval	-	-217.92, 15.31	-
p-value (3)	-	0.088	-

Note: The estimates for the 4th quarter were obtained from a repeated measurements model with treatment and quarter as factors, and treatment*quarter interaction. (1) two-sided simultaneous confidence intervals using Dunnett adjustment; (2) one-sided p-value with Dunnett's adjustment testing the hypothesis that the mean decrease in serum ferritin (µg/L) is not greater under deferasirox than under placebo. Critical alpha-level: 0.025; (3) two-sided p-value testing the hypothesis that the change in serum ferritin is identical in the 2 deferasirox groups. Critical alpha-level: 0.05. The last available quarter was carried forward if no value was available for any quarter.
Source: Table 6-5 of Attachment 3, Addenda Section B NTDT

Comparative harms

6.19 No comparative analyses of safety were reported within the publications. Potential side effects of treatment were largely inferred from clinical experience to date in other indications or were based on pre and post treatment data of single arm studies. It was anticipated that DFX treatment could be associated with more gastro-intestinal tract (GIT), renal and hepatic events and rash, mostly mild in nature, however severe adverse events such as acute renal failure, cytopenias and GIT haemorrhage (some fatal) were also reported. It was suggested that MDS patients who are older than the thalassemia patients may be more prone to certain side effects with DFX (such as increased serum creatinine) given they would likely have poorer renal and hepatic function. The discontinuation rates of DFX in MDS were also notably higher than in thalassemia patients.

6.20 With regards to the comparative harms associated with DFX in NTDT, the ESC noted the results of the THALASSA trial, whereby the majority of the events were of mild to moderate severity and were resolved on treatment. There was no discontinuation and the incidence of adverse events was similar across treatment groups.

Benefits/harms

6.21 A benefits and harms table for DFX in MDS was not able to be constructed as no RCTs were included in the submission to inform the comparative benefits and harms

of ICT versus no ICT, and the range of observational studies presented in the submission was not appropriate for this purpose.

Clinical claim

6.22 The submission described ICT and DFX as superior in terms of comparative effectiveness, and non-inferior in terms of comparative safety over no ICT. For safety, it was argued that while ICT and, more specifically, DFX have a different safety profile compared to no ICT, it was not likely to result in worse patient outcomes. The evaluation considered the claim with respect to comparative efficacy and safety may not be appropriate, as detailed in the Comparative efficacy and Comparative harms sections above.

6.23 Despite nominating the suite of 8 non-randomised trials as the best available evidence for effectiveness of ICT in MDS, the submission only incorporated the DFX efficacy estimate from the MORE IPD analysis of HR = [redacted] into the model. This decision to favour the MORE registry IPD analysis over the Mainous (2014) meta-analysis was justified by the submission on the basis that using this data addressed some of the concerns with bias in the non-randomised data sources as it allowed for controlling of some potential confounders.

6.24 The ESC noted that while the IPD analysis was adjusted for the influence of baseline confounders (i.e. age, sex, total RBC units transfused, number of comorbidities, ECOG and IPSS risk), issues of confounding remained:

- patient clinical status could have influenced the decision to initiate chelation in the first place;
- the MORE registry contained a mixture of prospective and retrospectively observed iron chelation start dates, with a subset of patients initiating ICT prior to registration;
- varying chelation times and time from diagnosis exposed the analysis to the effects of informative censoring and ascertainment bias; and
- no propensity adjustment was incorporated, which would have better controlled for baseline confounders.

Economic analysis

6.25 The submission presented a modelled cost-utility economic evaluation using variables reported in Section C of the commentary; the effect of no chelation was estimated from the IPD analysis from the MORE registry, and the overall survival of DFX chelated MDS patients was estimated from the 10% PBS sample. The ESC considered that given the lack of proper RCT data to confirm any treatment effect of ICT in MDS, the conduct of an economic evaluation was probably premature and inappropriate. The risk of bias with the results of the economic evaluations was also high and uncertain. Table 7 summarises the model structure and rationale.

Table 7: Summary of model structure and rationale

Time horizon	10 years in the model base case versus up to 5 years in the MORE registry and up to 8 years in the PBS 10% sample.
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis. The base case for the modelled economic evaluation had two health states, 'alive with MDS' and 'dead'. At entry to the model, a decision was made to start or not start chelation and the model follows these two cohorts, everyone starts in the 'alive with MDS' health state and may move to the 'dead' health state in each of the monthly cycles.
Cycle length	1 month (consisting of 30.4375 days)
Transition probabilities	The key transition is from the "alive with MDS" health state to "dead", this was estimated to be: - ICT treated: monthly rate of 0.018 which was equivalent to per cycle probability of: 0.0186, this was derived from a 10% PBS population who were treated with DFX, who were ≥55years at the time of their first script. Survival was estimated from time of first script to recorded death using extreme-value regression analysis. - Not ICT treated: monthly rate of [redacted]/ HR of [redacted] (i.e. 0.22 0.0238) equating to a per cycle probability of: [redacted]. The HR was derived from the MORE registry IPD analyses comparing patients who were treated with ICT and those that were not and adjusting for some potential confounders. - Half cycle corrections were applied to the time spent in each health state and the costs and complications of AML but not for the cost of DFX, which is assumed to occur for all patients at the start of each model cycle.
Discount rate	5% for costs and outcomes
Software package	Excel 2010, v.14.0

Source: constructed during the evaluation

6.26 Key drivers of the model are summarised in Table 8.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Assumed transition probabilities for chelated and non-chelated patients from alive with MDS to dead health states.	The transition probabilities were jointly determined from both the 10% PBS population (which informed the baseline risk of death in those treated with DFX) and the MORE registry data (informing the HR of ICT versus no ICT on survival).	High. If ICT does not impact on survival outcomes in MDS, then ICT treatment will be dominated by BSC. In addition, relatively small fluctuations in HR can cause a large change in the ICER.
Utility assumed for the MDS health state	Base case utility of 0.84 for 'alive with MDS' for both the ICT and no ICT patient groups (derived from Karnon 2008) for DFX in treatment of patient of iron overload. The ESC considered this utility to be unreasonable as it was derived in the context of children with thalassemia and was not applicable to the requested population and indication. During the evaluation, some additional references reporting relevant HRQoL in MDS were identified. Szende (2009)[1] reported the results of EQ-5D health state utilities for patients with MDS based on patients' transfusion status. A health state utility of 0.60 was estimated for patients who are transfusion dependent with MDS, which would also describe patients in the health state. The PSCR suggested another utility value of 0.78 from Szende et al (2009). Given the advanced age of the patients and the fact that they are transfusion dependent, the ESC considered that a utility value of 0.78 may be considered optimistic as well.	The model was sensitive to the assumed utility of patients with MDS.
Time horizon	10 years was assumed in the base case.	A shorter time horizon significantly increased the ICER.

Source: compiled during the evaluation

6.27 Results of the base case cost effective analysis are summarised in Table 9. The redacted table shows that the cost per QALY was $15,000 - $45,000 and the cost per life year gained was $15,000 - $45,000.

Table 9: Cost-effectiveness of ICT versus no ICT (BASE CASE) over 10 years

	ICT	No ICT	Difference
Discounted			
Cost	$[redacted]	$0	$[redacted]
LYG	3.491	2.953	0.538
QALYs	2.932	2.480	0.452
Cost per QALY			$[redacted]
Cost per LYG			$[redacted]

Abbreviations: ICT, iron chelation therapy; LYG, life year gained; QALY, quality adjusted life year gained.
Note: Sensitivity scenario s5A (in Sensitivity worksheet).

1 Szende A, Schaefer C, Goss TF, Heptinstall K, Knight R, Lübbert M, Deschler B, Fenaux P, Mufti GJ, Killick S, List AF, Valuation of transfusion-free living in MDS: results of health utility interviews with patients, Health Qual Life Outcomes. 2009 Sep 8;7:81. doi: 10.1186/1477-7525-7-81.

6.28 The results of univariate sensitivity analyses presented by the submission indicated that the model was most sensitive to the assumed treatment effect of DFX, and the assumed time horizon of the model. Additional univariate and multivariate analyses conducted during the evaluation found the model was also very sensitive to the assumed health state utility for MDS. When a time horizon of 6 years (based on the estimated median survival of patients with IPSS low risk MDS) and the utility value reported by Szende 2009 (0.6) was used in the model, the ICER increased to $45,000/QALY - $75,000/QALY. The ESC noted that the model was also sensitive to the HR.

6.29 The ESC noted the PSCR's argument that a utility value of 0.6 was too low as it was based on people having advanced disease and higher IPSS risk. The PSCR proposed a new utility of 0.78, the average utility of all patients in the Szende 2009 study, which resulted in an ICER of $15,000 - $45,000. The PSCR provided sensitivity analyses around this utility value.

6.30 While the ESC noted the PSCR's argument, it was considered that given the advanced age of the MDS population and the fact that they were transfusion dependent, a utility value of 0.78 may be still be optimistic. The ESC considered that the most plausible utility value lay somewhere between 0.6 and 0.78.

6.31 The model was also sensitive to the time horizon. Referring to the Markov trace in Figure D.5.1 of the Commentary, the ESC noted the proportion of patients in each health state of the model over 5-20 years and considered that for the MDS population, a time horizon between 6 years and the base case of 10 years would be more acceptable.

6.32 The ESC considered a number of sensitivity analyses varying the utility value and the time horizon and these are presented in Table 10.

Table 10: Results of the sensitivity analyses requested by ESC

Analyses	Incremental costs	Incremental effectiveness	ICER
Submission base case: utility (MDS) 0.84, time horizon 10 yrs	$[redacted]	0.452	$[redacted]
Utility (MDS) of 0.78 based on Szende 2009, overall population (b/c: 0.84)	$[redacted]	0.420	$[redacted]
Utility (MDS) of 0.6 based on Szende 2009, 'transfusion dependent' (b/c: 0.84)	$[redacted]	0.323	$[redacted]
Time horizon 6 yrs (b/c: 10 yrs)	$[redacted]	0.304	$[redacted]
Time horizon 6 yrs (b/c: 10 yrs) AND utility (MDS) of 0.78 based on Szende 2009, overall population (b/c: 0.84)	$[redacted]	0.283	$[redacted]
Time horizon 6 yrs (b/c: 10 yrs) AND utility (MDS) of 0.6 based on Szende 2009, 'transfusion dependent' (b/c: 0.84)	$[redacted]	0.217	$[redacted]

Abbreviations: MDS = myelodysplastic syndrome

6.33 The ESC accepted the ICER of $15,000 - $45,000, with a utility value of 0.78 and a time horizon of 10 years, as presented in the PSCR, as the sponsor's revised base case. However, the ESC remained concerned that both of these parameters (utility of 0.78 and time horizon of 10 years) were optimistic, and that the ICER was most likely between $15,000 - $45,000 and $45,000 - $75,000, the latter using the more conservative assumptions of 0.6 for the utility value and 6 years for the time horizon. The Pre-PBAC response asserted that as 0.75 was the most frequent utility for

transfusion dependent patients in Szende 2009, it would be the most pragmatic and reasonable estimate. The response also asserted that an 8 year time horizon would be appropriate, noting the submission model, where at 8 years approximately 10% of patients in the no ICT arm were still alive. This sensitivity analysis resulted in an ICER of $45,000 - $75,000.

6.34 The ESC noted that the model did not consider ongoing monitoring costs associated with chelation. While the PSCR stated that these may be small, the ESC considered that they were still important to consider as monitoring not only incurs a cost but may also mean that health complications unrelated to the chelation are more likely to be detected, which would also impact on costs.

6.35 The submission presented an additional sensitivity analysis exploring the impact of iron chelation on AML, using the MORE dataset alone. The ESC did not consider the impact of chelation on the subsequent development of AML was causatively supported by the existing evidence.

Drug cost/patient/day:

6.36 $[redacted] (estimated based on lifetime supply of DFX on PBS from a 10% PBS population), this was considered necessary as DFX is dosed based on body weight and serum iron ferritin levels and interruptions to treatment (to manage either side effects or iron ferritin levels) may be frequent.

Estimated PBS usage & financial implications

6.37 This submission was not considered by DUSC, however DUSC had previously reviewed the use of DFX on the PBS (in October 2014). The submission adopted a market share approach and examined the utilisation of DFX for the treatment of iron overload in three scenarios with the following associated prices for DFX:

Scenarios assessed	Price of DFX assumed in analyses
Scenario1: No change to the current PBS listing	Current price: inclusive of a [redacted]% rebate off Ex-Man prices
Scenario 2: The PBAC's (November 2014) proposed DFX PBS restriction is implemented.	Current price: inclusive of a [redacted]% rebate off Ex-Man prices
Scenario 3: A malignant and non-malignant PBS restriction is implemented, achieving same coverage as Scenario 1 (i.e. proposed listings 2a and 2b)	Price incorporating a higher discount of [redacted]% for usage in MDS and NTDT populations, giving an overall weighted rebate of [redacted]% off Ex-Man prices (i.e., an additional [redacted]% off compared to the current discount).

6.38 The estimated number of scripts and net cost to PBS for Scenario 3 (the proposed listing: 2a and 2b) is summarised in Table 11. This scenario assumes that 5% of patients currently accessing PBS treatments for MDS and NTDT will no longer be eligible, however, the proposed listing was sufficiently loose to permit all currently eligible patients to continue obtaining PBS supplies of DFX. The ESC noted the paper "Epidemiology of Myelodysplastic Syndromes" by Ma (2012)[2] which suggested that the incidence of MDS may be increasing due to an improved awareness of the disease and more thorough clinical work up; thus the ESC considered that the real number of scripts could be higher than the adjusted estimate presented in the Commentary.

[2] Ma, X. 'Epidemiology of Myelodysplastic Syndromes'. *Am J Med*. 2012 July ; 125(7 Suppl): S2–S5. doi:10.1016/j.amjmed.2012.04.014

Table 11: Estimated use and financial implications (number in brackets is the increment from Scenario 2, assuming the November 2014 PBAC recommendation is implemented)

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Estimated extent of use					
Total DFX scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS					
Net cost to PBS/RPBS[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] net of patient co-payment Source: Tables E.2-13 and E.2-15 of the submission.

The redacted table above shows that at year 5, the estimated total net cost to the PBS/RPBS would be $10-$20 million.

6.39 In Scenario 3, there was the potential for the net cost/year for the PBS to be greater than the estimate in the submission because: 1) there was the potential for the proportion of patients that will be accessing DFX under listing 2b to be greater than the 55% *predicted* by the submission; and 2) it was likely that the number of patients accessing PBS funded DFX will not reduce. The ESC noted the PSCR argument that this would be mitigated if tight wording around the restriction was ensured and the ESC accepted the PSCR suggested updates to the requested restriction.

6.40 In a sensitivity analysis, the submission assumed that in Scenario 2, 30% of patients no longer able to access DFX on PBS will switch to DFO. Using this assumption, the incremental cost for adopting the PBAC proposed DFX listing was estimated to be less than $10 million by Year 5 of listing (instead of less than $10 million) from Scenario 2. The ESC considered that as substitution to DFO could not be ruled out, this sensitivity analysis may be informative.

6.41 Based on the market research presented in the submission, the proportional use of DFX for MDS and NTDT was 60% of DFX's overall utilisation on the PBS (MDS: 55% and NTDT: 5%). This proportion was then used to estimate an overall weighted rebate for DFX (a higher rebate is offered for patients with MDS and NTDT). There was a lack of data on the prevalence of haemoglobinopathies in Australia. The DUSC analysis showed 59% of patients were born before 1960; resulting in at least 59% of current patients being treated for conditions other than thalassaemia due to high childhood mortality before 1960. Additionally, a proportion of patients born after 1960 are likely to be accessing deferasirox for conditions other than thalassaemia due to high rates of mortality in early adulthood.

Quality Use of Medicines (QUM)

6.42 Limited detail was provided in the submission on QUM activities. The main strategies appeared to be the provision of information to clinicians via letters, and guidance documents to assist with identification of eligible patients if the current listing was amended.

Financial Management – Risk Sharing Arrangements

6.43 The submission proposed additional rebates for use of DFX in the MDS and NTDT subpopulations. This would bring its overall weighted rebate to [redacted]% off the ex-manufacturer prices (i.e. an additional [redacted]% discount).

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

7 PBAC Outcome

7.1 The PBAC rejected the submission to retain the current PBS restriction for DFX for patients with " chronic iron overload in patients with disorders of erythropoiesis" as this very broad restriction enabled major use outside populations where cost-effectiveness has been demonstrated, in particular myelodysplasia. The PBAC did not accept that a survival benefit due to DFX therapy had been proved in MDS or malignant disorders and therefore the cost-effectiveness of DFX in MDS generally was not adequately demonstrated. However, the PBAC recognised that iron overload is a cause of major morbidity and mortality in patients with longer survival, such as those with NTDT and transfusion-dependent patients with very good prognosis MDS or good prognosis myelofibrosis. Under the restriction recommended by PBAC in November 2014, these patients could be significantly disadvantaged. Thus, the PBAC considered a revision to the restriction would be acceptable to allow use in these patient groups, noting the uncertainty of cost-effectiveness even in these subgroups.

7.2 The PBAC accepted best supportive care as the most relevant comparator. The PBAC clarified that the proposed restriction revision from November 2014 was to apply to DFX only and not the other PBS listed ICTs. The PBAC noted that the usage patterns of DFO were consistent with the indication and influenced by its method of administration, by injection, which minimised the use of DFO outside the PBS listing. The PBAC also considered that it was highly unlikely that DFO would replace DFX in the event it ceased being PBS-subsidised, and thus agreed with the submission that DFO was not a relevant comparator.

7.3 The PBAC discussed that in transfusion-dependent thalassemia, iron is the main driver of premature death, and iron chelation is highly effective and has revolutionised outcomes. In contrast, the use of ICT in MDS had not been established. The PBAC noted it was the subject of an ongoing randomised trial (TELESTO). The PBAC further noted that Lyons et al (2014, p.152) stated that "National Comprehensive Cancer Network guide-lines recommend the use of chelation therapy in iron-overloaded, lower-risk patients with MDS because of their longer predicted survival and the potential for developing organ damage secondary to iron overload. However, it is difficult to determine the contribution of iron toxicity to morbidity and mortality in these patients because of their advanced age and the high prevalence of comorbidities driving non-leukemic mortality."

7.4 While considering the clinical evidence, the PBAC noted that the discontinuation rates of DFX in MDS were notably higher than for thalassemia patients, and considered that as DFX has well known toxicities, the rate of discontinuation was likely to be heavily influenced by actual and perceived benefits.

7.5 The PBAC noted the numerous differences across the observational studies in MDS patients presented in the submission and considered that these differences introduced critical confounding which diminished the confidence that could be placed on the analysis outputs. The PBAC considered that the Lyons data was the most applicable. It noted that while these data showed a difference in overall survival in favour of ICT, the distribution of causes of death was unchanged, arguing against mortality differences being driven by iron overload. The PBAC also noted that many patients had been chelated for less than 6 months.

7.6 The PBAC also agreed with ESC that the submission's assertion that MDS patients undergoing ICT may be less likely to progress to AML was not causatively supported by the evidence provided.

7.7 The PBAC questioned the clinical benefit of DFX in high risk MDS, given the prognosis for these patients is very poor and unlikely to be improved with ICT. Similarly, the PBAC questioned the clinical benefit in intermediate risk MDS where the median survival is less than five years. Noting that the TELESTO trial has included patients with low and intermediate risk MDS, the PBAC considered that this position could be revisited upon the release of the TELESTO data.

7.8 The PBAC noted the letter of support for DFX in NTDT from the HSANZ, which stated that the proposed change to the DFX listing from the November 2014 meeting would exclude and deleteriously impact NTDT patients, who are at significant risk of morbidity from iron overload.

7.9 The PBAC accepted that there may be a survival advantage associated with DFX in NTDT, noting that in NTDT iron overload is the main driver of premature death; however the PBAC considered that it would be substantially less than that observed in transfusion-dependent thalassemia, given that the rate of iron accumulation is slower and more uncertain, and that the association with premature death is less established. The PBAC noted that in acknowledgement of this uncertainty, the sponsor had offered an additional rebate.

7.10 The PBAC noted that the NTDT population was small, that the doses required were generally low, that treatment was intermittent but long term, and that the treatment algorithm was clear.

7.11 After consideration of all the provided clinical evidence, and the invited input from HSANZ and ANZCHOG on ICT in MDS and other malignancies, the PBAC acknowledged that ICT may provide a clinical benefit to a small population of patients with malignant disorders of erythropoiesis with a median life expectancy of at least five years. The PBAC considered that excess mortality for these patients would be highly likely after 10 years of transfusion dependence without chelation, and that multi-organ morbidity was likely to occur up to 5 years earlier.

7.12 The PBAC noted that transfusion dependent malignant disorders of erythropoiesis with a median life expectancy of at least 5 years would include patients with low risk MDS and good prognosis myelofibrosis. The PBAC considered that this would be a small population.

7.13 For the economic evaluation in MDS, the PBAC agreed with ESC that given the uncertainty in the clinical evidence a formal economic evaluation was probably premature. PBAC also noted that the utility value used in the model was heavily dependent on patient selection and considered that as population make-up had been inadequately defined between the studies, it was difficult to determine an appropriate utility value with the evidence provided. The PBAC also considered that the appropriate time horizon for the base case was 10 years, given the inherent better prognosis for patients with low risk MDS. The PBAC also considered that the HR was a major driver of the model and that the HR favoured by the sponsor was highly uncertain.

7.14 The PBAC considered that base case ICER was optimistic and highly uncertain, given the deficiencies in the clinical data, and the additional concerns identified by ESC. Even if the MDS population was limited to patients with low risk disease only, the PBAC considered that the ICER would remain above the level of acceptability at the price requested.

7.15 The PBAC recommended that the following rebates on the ex-manufacturer price of DFX apply to the populations recommended for inclusion within the revised restriction to better reflect the major uncertainties in cost-effectiveness in the NTDT and MDS populations:
- [redacted]% for the transfusion dependent non-malignant thalassemias, as applied to the current PBS listing
- [redacted]% for the NTDT, as offered in the current submission (an increase from the current [redacted]% rebate)
- in the order of [redacted]% for the transfusion dependent malignant disorders (MDS and myelofibrosis) with a median life expectancy greater than five years.

The PBAC recommended that these rebates should form the basis of a new weighted effective ex-manufacturer price for DFX.

7.16 The PBAC noted the uncertainty regarding the estimated number of scripts, and considered the acceptance of a broader indication than recommended in November 2014 to fill an unmet need in a highly targeted population should be reviewed by DUSC and PBAC 12-24 months after PBS listing changes. The PBAC also acknowledged that some switching to DFO is possible, but considered it highly unlikely given that, historically, clinician preference for DFX over DFO has been driven by its more favourable route of administration (i.e. oral).

7.17 The PBAC recommended that the revised DFX restriction include patients with transfusion dependent thalassemias, NTDT and, subject to price negotiation, patients with transfusion dependent malignant disorders of erythropoiesis with a median life expectancy greater than five years. Revised restriction wording is prosed below in Section 8.

7.18 The PBAC considered that patients with very good prognosis MDS with a median life expectancy of greater than five years would fall under one or more of the following prognostic categories:
- Underlying MDS classified as low risk according to IPSS
- Underlying MDS classified as very good prognosis or good prognosis according to IPSS-R

- Underlying MDS classified as low or very low risk according to WPSS.

7.19 The PBAC agreed with ESC that the request for a S100 (Highly Specialised Drugs) listing was appropriate.

7.20 The PBAC recommended that the 20 Day Safety Net Rule should apply.

7.21 The PBAC recommended that deferasirox should not be treated as interchangeable on an individual patient basis with any other drug, according to s101(3BA) advice.

7.22 The PBAC advised that deferasirox is suitable for prescribing by nurse practitioners as continuing treatment only under a shared care model.

7.23 The PBAC noted that this submission is not eligible for an Independent Review given that the Committee approved a change to the restriction.

7.24 The PBAC recommended that this listing be reviewed by the DUSC and PBAC in 2019.

Outcome:
Rejected

Following the conclusion of the July 2015 meeting, the sponsor made an appropriate price offer for patients with malignant disorders of erythropoiesis with a median life expectancy greater than five years.

The PBAC advised that the revised restriction recommended at the July 2015 meeting would be implemented following its finalisation and would include the following populations:

- patients with transfusion dependent non-malignant disorders of erythropoiesis;
- patients with NTDT; and
- patients with transfusion dependent malignant disorders of haemopoiesis with a median life expectancy greater than five years.

The PBAC also noted that the description of very good prognosis myelodysplasia with a median life expectancy of greater than five years (outlined in paragraph 7.18 of the minutes) required a correction. The PBAC considered that the appropriate terminology for the intended groups defined by the IPSS-R score should be either very low risk or low risk, noting that the very good prognosis and good prognosis stated in the minutes referred to cytogenic scoring only, rather than the overall IPSS-R score. This change has been reflected in the revised recommended restriction.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

Chronic iron overload in patients with transfusion dependent non-malignant disorders of erythropoiesis: Public and Private (Initial)

Name, Restriction, Manner of administration and form	Max.Qty	№.of Rpts	Proprietary Name and Manufacturer
DEFERASIROX			
125 mg tablet: dispersible, 28	6	5	Exjade® NV
250 mg tablet: dispersible, 28	6	5	
500 mg tablet: dispersible, 28	6	5	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must not have a malignant disease

Chronic iron overload in patients with transfusion dependent non-malignant disorders of erythropoiesis: Public and Private (Continuing)

Name, Restriction, Manner of administration and form	Max.Qty	No. of Rpts	Proprietary Name and Manufacturer
DEFERASIROX			
125 mg tablet: dispersible, 28	6	2	Exjade® NV
250 mg tablet: dispersible, 28	6	2	
500 mg tablet: dispersible, 28	6	2	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload

Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised therapy with this drug for this condition.

Chronic iron overload in patients with non-transfusion dependent thalassaemia: Public and Private (initial)

Name, Restriction, Manner of administration and form	Max.Qty	№.of Rpts	Proprietary Name and Manufacturer
DEFERASIROX			
125 mg tablet: dispersible, 28	6	5	Exjade® NV
250 mg tablet: dispersible, 28	6	5	
500 mg tablet: dispersible, 28	6	5	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must not have a malignant disease

Chronic iron overload in patients with non-transfusion dependent thalassaemia: Public and Private (Continuing)

Name, Restriction, Manner of administration and form	Max.Qty	No. of Rpts	Proprietary Name and Manufacturer
DEFERASIROX			
125 mg tablet: dispersible, 28	6	2	Exjade® NV
250 mg tablet: dispersible, 28	6	2	
500 mg tablet: dispersible, 28	6	2	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised therapy with this drug for this condition.

Chronic iron overload in patients with transfusion-dependent malignant disorders of haemopoiesis and a median life expectancy exceeding five years: Public and Private (Initial)

Name, Restriction, Manner of administration and form	Max.Qty	No. of Rpts	Proprietary Name and Manufacturer
DEFERASIROX			
125 mg tablet: dispersible, 28	6	2	Exjade® NV
250 mg tablet: dispersible, 28	6	2	
500 mg tablet: dispersible, 28	6	2	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload
Treatment phase:	Initial

Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must be red blood cell transfusion dependent. AND Patient must have a serum ferritin level of greater than 1000 microgram/L. AND Patient must have a median life expectancy exceeding five years.
Administrative Advice	A patient's median life expectancy is determined by the severity of their underlying disease. Patients with underlying myelodysplastic syndrome are considered to have a median life expectancy exceeding five years if they are classified as: - low risk according to the International Prognostic Scoring System (IPSS); or - very low and low risk according to the Revised International Prognostic Scoring System (IPSS-R); or - very low and low risk according to the WHO classification based Prognostic Scoring System (WPSS). Patients with underlying myelofibrosis have a median life expectancy exceeding five years if they are classified as: - low or intermediate risk according to the International Prognostic Scoring System (IPSS); or - low or intermediate-1 risk according to Dynamic International Prognostic Scoring System (DIPSS).

Chronic iron overload in patients with transfusion-dependent malignant disorders of haemopoiesis with a median life expectancy greater than five years: Public and Private (Continuing)

Name, Restriction, Manner of administration and form	Max.Qty	No. of Rpts	Proprietary Name and Manufacturer
DEFERASIROX			
125 mg tablet: dispersible, 28	6	2	Exjade® NV
250 mg tablet: dispersible, 28	6	2	
500 mg tablet: dispersible, 28	6	2	

Category / Program	Section 100 – Highly Specialised Drugs Program (Public) Section 100 – Highly Specialised Drugs Program (Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Condition:	Iron overload
PBS Indication:	Chronic iron overload
Treatment phase:	Continuing

Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised therapy with this drug for this condition
Administrative Advice	Interruption of treatment should be considered if serum ferritin levels fall consistently below 500 microgram/ml.

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

Novartis appreciates the opportunity to work with the PBAC to ensure continuity of care for deferasirox patients with MDS and NTDT.