All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Deferasirox (Exjade®▼) for the treatment of chronic iron overload due to blood transfusions

Novartis Pharmaceuticals Ltd

Advice No: 0808

Recommendation of AWMSG

Deferasirox (Exjade®▼) is recommended for use within NHS Wales for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. It is also recommended for the treatment of chronic iron overload due to blood transfusions when desferrioxamine (DFO) therapy is contraindicated or inadequate in the following patient groups:

- in patients with other anaemias,
- in patients aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7 ml/kg/month of packed red blood cells).

Deferasirox (Exjade®▼) is not suitable for shared care within NHS Wales.

This report should be cited as:

The All Wales Medicines Strategy Group Final Appraisal Report
deferasirox (Exjade®▼) - June 2008

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Friday, 13th June 2008

The recommendation of AWMSG is:

Deferasirox (Exjade®▼) is recommended for use within NHS Wales for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. It is also recommended for the treatment of chronic iron overload due to blood transfusions when desferrioxamine (DFO) therapy is contraindicated or inadequate in the following patient groups:

- in patients with other anaemias,
- in patients aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7 ml/kg/month of packed red blood cells).

Deferasirox (Exjade®▼) is not suitable for shared care within NHS Wales.

Additional note:

- There are limited data and the cost-effective case is less secure for the use of deferasirox in patients with myelodysplastic syndrome.
- Treatment with deferasirox should be initiated and maintained by specialists experienced in the treatment of chronic iron overload due to blood transfusions. The specialist nature of the underlying transfusion-dependent anaemias and resultant monitoring would suggest that deferasirox is unsuitable for shared care.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:

Deferasirox (Exjade®▼) is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. It is also indicated for the treatment of chronic iron overload due to blood transfusions when desferrioxamine (DFO) therapy is contraindicated or inadequate in the following patient groups:

- in patients with other anaemias,
- in patients aged 2 to 5 years,
- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7 ml/kg/month of packed red blood cells)[1].

2.2 Dosing:

Deferasirox is taken orally once daily as dispersible tablets. The recommended initial daily dose is 20 mg/kg body weight, but doses of 10 or 30 mg/kg may be considered depending on body iron levels and packed red blood cell volumes received. For patients already well managed on treatment with DFO, a starting dose of deferasirox that is numerically half that of the DFO dose could be considered (e.g. a patient receiving 40 mg/kg/day of DFO for 5 days per week [or equivalent] could be transferred to a starting daily dose of 20 mg/kg/day of deferasirox). Doses above 30 mg/kg are not recommended[1].

2.3 Market authorisation date: EU marketing authorisation was granted on 28th August 2006[2].

2.4 UK Launch date: Deferasirox was launched in the UK in September 2006[2].

3.0 DECISION CONTEXT

Iron accumulation is a serious complication in the management of patients who require regular blood transfusions. Without specific iron chelation therapy (ICT), almost all regularly transfused patients will develop iron toxicity in three to ten years, which may include liver and other organ disease, and endocrine disorders. Premature death occurs mainly due to cardiac complications[3,4].

Deferasirox is a tridentate iron chelating agent that forms a soluble complex with the Fe^{3+} ion in a 2:1 ratio[3]. Although deferasirox has orphan drug status[3], it does not fall within the ultra orphan drug category as defined by the AWMSG.

There are two other iron chelating agents licensed in the UK, each with different licensed indications:

DFO is usually administered by subcutaneous infusion (via portable infusion pump) over eight to 12 hours on 4–7 days per week. It has the broadest licensed indications of the three available agents, which include the treatment of chronic iron overload (amongst other indications)[5]. DFO has been the standard ICT for chronic iron overload for many years and has been demonstrated to improve morbidity and mortality. However, the demanding treatment regimen may lead to patient compliance issues and suboptimal treatment[3].

Deferiprone is administered orally three times per day[6]. Due to limited efficacy and safety data[3], it is indicated only for the treatment of iron overload in patients with thalassaemia major when DFO therapy is contraindicated or inadequate[7]. Its adverse effect profile means it is not widely used in clinical practice[4].

Beta thalassaemia, sickle cell disease (SCD) and myelodysplastic syndrome (MDS) are the most common transfusion-dependent disorders that lead to iron overload. Beta thalassaemia typically affects people of Mediterranean, Middle-eastern and Asian origin, and SCD typically affects those of African or Hispanic origin. MDS mainly develops in people over the age of 60 years[4,8]. The company submission estimates that around 610 patients in Wales currently have one of these conditions (74 with beta thalassaemia, 74 with SCD and 462 with MDS). Of these, around 142 patients (23%) are estimated currently to receive ICT[8].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The main efficacy data comes from study 107, a phase III trial conducted in 591 patients with transfusion dependent beta thalassaemia. This study failed in its primary endpoint of showing that deferasirox was non-inferior to DFO in the proportion of all patients achieving treatment success as measured by liver iron concentration (LIC). This was possibly due to an imbalance in doses between the two agents in patients with baseline LIC < 7 mg Fe/g dry weight (dw), which favoured DFO. *Post hoc* analyses indicated that deferasirox at a dose of around 20 mg/kg/day was non-inferior to DFO in those patients (69% of the per protocol population) with a baseline LIC $\geq$7 mg Fe/g dw. These findings were generally replicated in study 108 (a non-comparative study in patients with mixed anaemia types, including patients with beta thalassaemia who were inadequately treated with DFO), and study 109 (a phase II trial of deferasirox against DFO in patients with SCD).

Serious adverse events were similar in the deferasirox and DFO groups, and were mainly related to skin effects, gastrointestinal (GI) effects and increases in liver enzymes. However, pooled data indicate that around 36% of patients treated with deferasirox experienced dose-related increases in serum creatinine levels of >33%, which in many cases did not return to normal upon dose reduction. In study 107, 9.7% of patients (versus 3.1% in the DFO group) also experienced abnormal creatinine clearance (< 90ml/min).

4.2 Review of the evidence on cost-effectiveness

The company's submission describes a cost-utility analysis of deferasirox at a dose of 20–30 mg/kg/day compared with DFO at doses of ≥35 mg/kg/day (i.e. the initial doses used in patients with baseline LIC > 7 mg Fe/g dw in the clinical trials) given over one year in three patient groups: beta thalassaemia, SCD and MDS.

In the base case analysis, the model predicts that deferasirox treatment would be associated with lower annual costs and greater utility than DFO treatment in patients with beta thalassaemia and SCD. In MDS patients, the incremental cost per QALY gained is estimated as £7,219. There are some issues which introduce bias and uncertainty in these estimates. The model considers the cost effectiveness of deferasirox over one year but ICT treatment is life long. The model is particularly sensitive to the assumptions around the type of infusion device used to deliver DFO. In addition, the licensed indications for deferasirox imply that it is only indicated for use in patients with SCD or MDS when DFO is contraindicated or inadequate. However, the model compares deferasirox against DFO in these patients, which precludes assessment of its cost effectiveness in those cases where DFO is not /no longer considered an appropriate treatment option.

5.0 LIMITATIONS OF DECISION CONTEXT:

- In contrast to DFO, there are no morbidity or mortality data available for deferasirox. The main efficacy measure used in studies to date is LIC, which is a surrogate marker of disease, and there are some issues with the techniques that have been used to measure this.
- Deferasirox has been studied only in patients with baseline serum creatinine within the age-appropriate normal range.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company submission describes a pivotal phase III study of deferasirox compared with DFO in the management of iron overload in patients with beta thalassaemia. Two supporting phase II studies (one in patients with SCD and one in mixed anaemia types) are also included. Interim data from three other studies involving patients with MDS are also provided[8], but are only briefly discussed here.

6.1.1 Study 107: Pivotal phase III non-inferiority study of deferasirox versus DFO in patients with beta thalassaemia

This was a one-year, multinational, open-label, phase III, non-inferiority study in paediatric (≥2 years of age) and adult patients with beta thalassaemia who required eight or more blood transfusions per year and were DFO experienced or ICT-naïve. Exclusion criteria included elevated liver enzymes, serum creatinine greater than the upper limit of normal, hepatitis infection, and documented poor response to DFO, or DFO toxicity[9].

Five hundred and ninety one patients were randomised (1:1) to deferasirox or DFO, of which 586 received treatment. Around 51% were aged less than 16 years, and 10% were aged less than six years. Doses were based on baseline liver iron concentration (LIC) (see table 1), which was measured by liver biopsy in the majority of patients (approximately 84%) or the non-invasive superconducting quantum interference device (SQUID) in those unable to undergo liver biopsy (approximately 16% of patients). At baseline, the mean LIC across all patients was 13.7 mg Fe/g dw. The initial dose was to remain unchanged throughout the study unless efficacy and safety markers indicated dose adjustment was necessary[9].

Table 1. Initial assigned doses based on LIC and average (±SD) doses actually received in study 107[9]

Baseline LIC	**Deferasirox dose (mg/kg/day) (N=296)**	**DFO dose (mg/kg, 5 days/week)** (N=290)**
2–3 mg Fe/g dw *	Assigned dose: 5 (N=15)	Assigned dose: 20–30 (N=14)
	Mean: 6.2 ± 1.6 Median: 5.0	Mean: 33.9 ± 9.9 Median: 30.0
> 3– 7 mg Fe/g dw *	Assigned dose: 10 (N=78)	Assigned dose: 25–35 (N=79)
	Mean: 10.2 ± 1.2 Median: 10.0	Mean: 36.7 ± 9.2 Median: 35.0
> 7–14 mg Fe/g dw	Assigned dose: 20 (N=84)	Assigned dose: 35–50 (N=91)
	Mean: 19.4 ± 1.7 Median: 20.0	Mean: 42.4 ± 6.6 Median: 40.8
> 14 mg Fe/g dw	Assigned dose: 30 (N=119)	Assigned dose: ≥ 50 (N=106)
	Mean: 28.2 ± 3.5 Median: 30.0	Mean 51.6 ± 5.8 Median: 51.0
*patients in these LIC groups assigned to DFO could continue on their current DFO dose **Actual number of days of DFO administration ranged 3–7 per week. Doses have been transformed to 5 days/ week equivalents.		

The primary efficacy endpoint of the study was a binary outcome indicating the success or failure of therapy at one year. Depending on LIC at baseline, different objectives had to be met to achieve success:

- For patients with baseline LIC within the range of 2 to <7 mg Fe/g dw, success was defined by the LIC at the end of the study being in the range 1 to <7 mg Fe/g dw.
- For patients with baseline LIC within the range of ≥7 mg to <10 mg Fe/g dw, success was defined by the LIC at the end of the study being in the range 1 to <7 mg Fe/g dw.
- For patients with baseline LIC ≥10 mg Fe/g dw, success was defined by a reduction of at least 3 mg Fe/g dw.

Deferasirox was to be considered non-inferior to DFO if the lower limit of the two-sided 95% confidence interval (95% CI) for the difference in the percentage of patients achieving treatment success (deferasirox – DFO) was above -15%. This was based on

analysis of the per protocol population, which included patients who received study drug and had a LIC measurement at baseline and at the end of the study using the same technique. Intention to treat (ITT) analysis was also performed. Secondary endpoints included absolute changes in LIC, serum ferritin and change in body iron burden as reflected by the ratio of iron excretion to iron intake.

Results for the primary efficacy analysis of study 107
Deferasirox failed to meet the criterion for non-inferiority to DFO in the primary efficacy population (n=553). The lower limit of the 95% CI for the difference in the percentage achieving treatment success exceeded 15% in the per protocol population (success with deferasirox 52.9% versus DFO 66.4%, difference -13.5% [95% CI -21.6 to -5.4])[3].
In a *post hoc* analysis of the subpopulation with a baseline LIC ≥7 mg Fe/g dw (n=381), success rates were comparable for deferasirox and DFO (58.6% versus 58.9%) and non-inferiority was achieved (difference -0.3% [95% CI -10.2 to +9.6]). These patients made up the majority (approximately 69%) of the primary efficacy per protocol population and received deferasirox at doses of around 20 mg/kg/day or more (see Table 2)[3]. Results for the subpopulation with baseline LIC < 7 mg Fe/g dw are in Appendix 1, Table 1A.

Table 2. Success rates based on LIC in the primary efficacy analysis and the subpopulation with LIC ≥ 7 mg Fe/g dw in study 107[3,9]

	Deferasirox N=276	**DFO N=277**
Primary efficacy per protocol population	**n=276**	**n=277**
Success rate (n [%])	146 (52.9)	184 (66.4)
95% CI	[47.0 to 58.8]	[60.9 to 72.0]
Absolute percentage difference (deferasirox-DFO) and 95% CI	**-13.5% [-21.6 to -5.4]**	
LIC ≥ 7 mg Fe/g dw	**n=191**	**n=190**
Success rate (n [%])	112 (58.6)	112 (58.9)
95% CI	[51.7 to 65.6]	[52.0 to 65.9]
Absolute percentage difference (deferasirox-DFO) and 95% CI	**-0.3% [-10.2 to 9.6]**	

Results for secondary efficacy analyses of study 107
As with the primary efficacy analysis, a dose response relationship for deferasirox is apparent for the secondary efficacy analysis[3].

In patients with baseline LIC < 7 mg Fe/g dw, deferasirox at a dose of 5 or 10 mg/kg/day was unable to prevent iron accumulation as measured by the absolute change in LIC, serum ferritin and change in body iron balance (ratio of iron excretion to iron intake). In patients who received DFO at a median dose of 30 or 35 mg/kg/day, the iron burden as measured by these parameters was also increased, but to a lesser degree than with deferasirox (see Appendix 1, Table 2A)[3].

The changes in these secondary efficacy parameters in those with a baseline LIC ≥7 mg Fe/g dw (n=371) are presented in Table 3. These data suggest that, in those with a LIC in the range >7 to ≤14 mg Fe/g dw, deferasirox at a dose of 20 mg/kg/day maintains the iron burden, and in those with a LIC >14 mg Fe/g dw, deferasirox at a dose of 30

mg/kg/day reduces the iron burden. There was no significant difference in absolute change in LIC between patients treated with deferasirox and DFO, and there were no marked differences in the ratio of iron excretion to iron intake between the treatment groups. Serum ferritin levels mirrored the changes observed with LIC[3,9].

Table 3. Absolute changes in secondary endpoints in patients with baseline LIC >7mg Fe/g dw in study 107 (per protocol population)[3,9]

LIC in mg Fe/g dw	Median dose mg/kg/day		Iron burden at EOS (based on available values)	n	Mean ± SD deferasirox	n	Mean ± SD DFO
	Deferasirox	DFO					
LIC > 7-14	20	41	Change in serum ferritin (ng/ml)	80	-36 ± 721	89	-364 ± 614
			Change in LIC (mg Fe/g dw)	77	-0.4 ± 4.70	87	-1.9 ± 2.93
			Ratio iron excretion:intake	77	1.02 ± 0.398	87	1.13 ± 0.241
LIC > 14	30	51	Change in serum ferritin (ng/ml)	115	-926 ± 1416	101	-1003 ± 1428
			Change in LIC (mg Fe/g dw)	108	-8.9 ± 8.07	98	-6.4 ± 6.93
			Ratio iron excretion:intake	108	1.67 ± 0.716	98	1.44 ± 0.596

Points to note

- An open-label design is appropriate given the different administration requirements for the two treatments and the difficulties this poses for blinding.
- Liver biopsy is the gold standard method for assessment of LIC. The SQUID method was used to assess LIC in patients unable to undergo liver biopsy. It appeared that the SQUID method underestimated LIC by 50% as compared to the values obtained from liver biopsy in this trial. This may have resulted in errors in assigning some patients to baseline LIC groups and initial drug doses, and categorisation of treatment as success or failure[3]. This would be a particular issue in the paediatric population in which SQUID was used most frequently. In the per protocol efficacy population, SQUID was used in approximately 37% of patients who were categorised as having a baseline LIC < 7 mg Fe/g dw, and in approximately 7% of those categorised as having a baseline LIC $\geq$ 7 mg Fe/g dw[3].
- The actual dose of DFO received by patients with baseline LIC < 7 mg Fe/g dw was often greater than that to which they were initially assigned (see Table 1), due to the protocol specifications on dose adjustment. This created an imbalance in doses between the two agents, which favoured DFO. This could in part explain why non-inferiority was not achieved in this sub group and in the overall per protocol population[3].
- The recommended initial dose of deferasirox is 20 mg/kg/day, although doses of 10 or 30 mg/kg/day may be considered depending on body iron levels and packed red blood cell volumes received[1]. Patients with baseline LIC <7 mg Fe/g dw received doses of 5 or 10 mg/kg/day. This study does not provide data on the use of doses of 20 mg/kg/day or more in patients with baseline LIC <7 mg Fe/g dw.
- Around a third of patients in both treatment groups required dose adjustment[8].

- The use of the binary outcome measure in this study, and the definitions of success or failure, could mask a range of true effects. For example, a patient with a decrease in LIC from 6.9 to 1.0 mg Fe/g dw and a patient with an increase in LIC from 2.0 to 6.9 mg Fe/g dw would both be classed as treatment "successes"[3].
- This study does not provide direct evidence of morbidity and mortality benefits for patients treated with deferasirox.
- This study excluded those with documented poor response to, or previous toxicity with, DFO[3,9] and so does not provide direct evidence of benefit with deferasirox in these patients. Patients with markers of renal impairment were also excluded.

6.1.2 Supporting studies

6.1.2.1 Study 109: Phase II safety study of deferasirox versus DFO in patients with SCD

This was a multicentre, open-label, phase II safety study in which efficacy was a secondary objective. Adult and paediatric (≥2 years of age) patients (n=203) with SCD who had developed transfusional iron overload and were either ICT-naïve or had received DFO for at least four weeks were randomised (2:1) to deferasirox or DFO treatment at doses based on their baseline LIC. Assigned doses were as in study 107 (Table 1) and LIC was assessed at baseline, week 24 and week 52 using SQUID. Mean LIC at baseline in the 195 patients who received therapy was 9.3 mg Fe/g dw. Around 50% of patients were aged less than 16 years, and around 4% were aged less than 6 years[3,8,10].

In the per protocol population (n=167), the mean reduction in LIC from baseline was reportedly statistically significant for both deferasirox (1.5 mg Fe/g dw [95% CI 1.0 to 2.1], p<0.001) and DFO (1.0 mg Fe/g dw [95% CI 0.1 to 1.8], p=0.022) at 52 weeks. There was no significant difference in the LIC change from baseline between the deferasirox and DFO groups. These results appear to be driven by patients with baseline LIC ≥ 7 mg Fe/g dw (n=97), as there was no significant change from baseline in either treatment group for patients with baseline LIC < 7 mg Fe/g dw. In those patients with baseline LIC ≥ 7 mg Fe/g dw, statistically significant mean reductions from baseline were seen for both deferasirox (2.3 [95% CI 1.4 to 3.1], p<0.001) and DFO (2.0 [95% CI 0.6 to 3.4], p=0.007), again with no significant difference between treatment groups. Changes in serum ferritin and the ratio of iron intake to excretion were generally compatible with these findings (although a marked change from baseline in serum ferritin in the deferasirox group was only seen at a median dose of 30 mg/kg/day)[8]. However, these data are not verifiable from the reference cited[10].

Overall, these data would suggest that, in those with baseline LIC < 7 mg Fe/g dw, deferasirox at a dose of ≤10 mg/kg/day (and DFO at the corresponding dose) maintained the mean LIC, and in those with a baseline LIC ≥ 7, deferasirox at a dose of ≥20 mg/kg/day reduced the mean LIC. No data from the ITT population have been presented in the company submission.

6.1.2.2 Study 108: Phase II single-arm study in mixed anaemia disorders
This was a multicentre, non-comparative study of deferasirox conducted in adult and paediatric patients with beta thalassaemia who were inadequately treated with DFO (n=85), and patients with MDS (n=47) and other rare anaemia disorders (n=52) who were either DFO-experienced or ICT-naïve. Inadequate treatment with DFO in patients with beta thalassaemia was defined as non-compliance (patients taking <50% of their DFO doses in the previous 12 months and with LIC $\geq$ 14 mg Fe/g dw), unacceptable DFO toxicity or contraindications, or poor response to DFO despite proper compliance and a LIC $\geq$ 2 mg Fe/g dw. Deferasirox doses were assigned as in study 107 (Table 1) and LIC was measured by liver biopsy (65%) or SQUID (35%) after one year[8]. At baseline, the mean LIC across all patients was 21.0 mg Fe/g dw. The same definitions of treatment success as in study 107 were used and the primary endpoint was considered to have been achieved if the lower limit of the 95% CI for the success rate exceeded 50% in the ITT population. Around 80% of patients were adults, mostly aged between 16 and 50 years (around 16% of patients were aged over 65 years)[8,11].

The primary endpoint in the ITT population was not achieved as the lower limit of the 95% CI for success rate was below 50% (success rate 50.5% [95% CI 43.3 to 57.8], p=0.441). The company submission suggests this may be due to inadequate dosing in patients with baseline LIC <7 mg Fe/g dw. These patients made up 5% of the entire study population. In the subpopulation with LIC $\geq$7 mg Fe/g dw in who LIC was measured by biopsy (n=113) the success rate was statistically significant (59.3% [95% CI 50.2 to 68.4], p=0.024), but not in the wider population in which LIC was measured by liver biopsy or SQUID (n=159) (52.2 [95% CI 44.4 to 60.0], p=0.289). The published paper for this study indicates that LIC values determined by SQUID had been doubled, to account for the fact that SQUID underestimates LIC levels by 50% compared with the gold standard of liver biopsy. Furthermore, this paper indicates that the significance of the results remains unaffected if SQUID data are excluded from the analyses altogether and only LIC data derived from biopsy are included[11]. As success rates obtained in those whose LIC was measured by biopsy are not verifiable from the reference cited, it is not possible to verify the biopsy determined success rates as reported in the company submission[8].

A breakdown of results by the underlying anaemia type is provided (Appendix 1, Table 3A) but should be interpreted with some caution, given the small number of patients in each group. In patients with beta thalassaemia (88% previously inadequately treated with DFO) and baseline LIC $\geq$ 7 mg Fe/g dw, the success rate when LIC was measured by biopsy or SQUID (n=70) was 61% (95% CI 50.0 to 72.8). Secondary endpoints of change from baseline in LIC, serum ferritin and iron balance generally followed the same dose response patterns as previously seen.

6.1.2.3 Interim data from studies involving patients with MDS
COMMERCIAL IN CONFIDENCE

6.2 Safety:
In the pivotal phase III study 107, in patients with beta thalassaemia, the overall rates of adverse events were similar for deferasirox and DFO (85.8% [254/296] versus 84.8% [246/290], respectively). Those adverse events reported more frequently with deferasirox than DFO included: abdominal pain (13.9% versus 9.7%), diarrhoea (11.8% versus

7.2%), nausea (10.5% versus 4.8%), rash (8.4% versus 3.1%), arthralgia (7.4% versus 4.8%), dyspepsia (3% versus 1.7%) and hepatobiliary disorders (4.7% versus 1.7%). Similar patterns of deferasirox adverse events were seen across the other studies and anaemia types[3]. Additional data provided as commercial in confidence.

Pooled data indicate that around 36% of patients treated with deferasirox experienced increases in serum creatinine levels of >33%. These were dose related, occurring mainly at doses of 20 or 30 mg/kg/day. In study 107, increases in creatinine levels of more than 33% were observed in 38.2% of deferasirox recipients compared with 14.2% for DFO. Creatinine levels remained within the normal range for the majority of patients (increases to levels above the upper limit of normal (ULN) were seen in 2.4% versus 0.3%, respectively). Dose adjustment or treatment interruption due to increases in creatinine occurred in 11.1% versus 0%, although the study protocol did not stipulate dose reduction for DFO recipients who experienced elevations in creatinine levels[3].

Pooled data indicate that deferasirox dose reduction led to a decrease in the serum creatinine levels in around 40% of cases where it was elevated, but levels still remained raised compared with baseline in most patients. In around 50% of cases, dose reduction led to a stabilisation of elevated creatinine levels, rather than a reduction. In study 107, 9.7% of patients (versus 3.1% in the DFO group) also experienced abnormal creatinine clearance (< 90ml/min)[3]. Cases of acute renal failure have been reported following post-marketing use of deferasirox[1].

Serious adverse events in study 107 were similar in the deferasirox and DFO groups (9.1% versus 8.6%). These were mainly related to skin effects, GI effects and increases in liver enzymes. Permanent discontinuations due to adverse events were low in both groups (2.7% versus 1.4%), but dose reductions due to adverse events were required more frequently with deferasirox than DFO (31.1% versus 18.6%)[3].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

DFO is the appropriate comparator for deferasirox. It has the broadest licensed indication in the treatment of chronic iron overload, is supported by evidence of morbidity and mortality benefits, and has been the standard ICT for many years[3].

7.2 Comparative effectiveness issues:

- In the one-year pivotal phase III study (107), and in the supporting phase two studies (108,109), efficacy has been assessed by measuring effects on LIC using liver biopsy or SQUID. Although LIC measured by biopsy may be considered a reference standard for assessment of the degree of iron overload, it cannot be used routinely for monitoring purposes in clinical practice. SQUID is not a validated tool for routine use and has been shown to underestimate LIC. This may have resulted in errors in assigning some patients to baseline LIC groups and initial drug doses, and categorisation of treatment as a success or failure. Serum ferritin is usually used for monitoring iron burden in clinical practice, although factors other than iron burden may influence serum ferritin levels.

- Deferasirox was found to be non-inferior to DFO in study 107 in beta thalassaemia patients with baseline LIC ≥ 7 mg Fe/g dw who were assigned to deferasirox doses of ≥ 20 mg/kg/day. This was a *post hoc* analysis, and non-inferiority was not achieved in the primary efficacy population. This may have been because the dose of deferasirox was insufficient relative to DFO in those with baseline LIC < 7 mg Fe/g dw. The same dose schedule for deferasirox was used in patients in studies 108 and 109, which also found that treatment met the defined success criteria only in those with baseline LIC ≥7 mg Fe/g dw. These trials provide no information on the use of deferasirox at an initial dose of 20 mg/kg/day in patients with baseline LIC < 7 mg Fe/g dw.
- Small sub studies are reported to have also demonstrated improvements in cardiac iron concentration with deferasirox (and DFO)[8]. This and the efficacy measures used in the clinical trials of deferasirox above are surrogate measures of effectiveness. Long term efficacy data are being collected and are reported to demonstrate sustained reductions in iron burden over a median of 3.5 years. However, unlike DFO, deferasirox has not yet been demonstrated to improve morbidity or mortality in iron overloaded patients.
- MDS patients are the largest source of ICT-eligible patients in Wales, although not all patients with MDS are suitable candidates for regular blood transfusions and ICT[12]. Study 108 and the interim results of studies US02, US03 and 2409 provide efficacy data that appears compatible with the efficacy demonstrated for deferasirox in other types of anaemia; however, there are no direct comparative data for deferasirox against DFO in patients with MDS. The company submission asserts that comparative trials of deferasirox against DFO are not ethical[8].
- DFO has been in clinical use for around 40 years[4] and its adverse effect profile is well known. Safety data for deferasirox is still relatively immature. The clinical trials programme identified issues around adverse gastrointestinal, skin, and renal effects, despite the fact that patients with signs of renal impairment were excluded from the trials. Around 36% of those treated with deferasirox experienced an increase in serum creatinine levels, about two-thirds of which returned below the 33% level without dose adjustment. In the remaining third, the serum creatinine increase did not always respond to a dose reduction or a dose interruption, and complete recovery was rare. The long term consequences of renal toxicity with deferasirox are unknown[3], and cases of acute renal failure have been reported following its use in clinical practice[1]. Weekly serum creatinine and creatinine clearance monitoring in the first month of treatment initiation or adjustment are recommended, with monthly monitoring thereafter. Tests for proteinuria and liver function tests also should be performed monthly[1].
- The DFO treatment regimen is demanding and may lead to suboptimal compliance. The oral route of administration for deferasirox may be more convenient for patients and is free of the potential risks associated with parenteral administration. Other studies are reported to demonstrate greater preference for[13], and improvements in quality of life[14] with, deferasirox compared with DFO (see section 8).
- It should be noted that the licensed indications for deferasirox imply it is a first line treatment only in patients aged ≥6 years with beta thalassaemia. It is

indicated for the treatment of chronic iron overload due to blood transfusions in other circumstances only when DFO is contraindicated or inadequate[1].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by the use of deferasirox in its licensed indications justify any associated increase in costs over DFO and whether the total budgetary impact of supporting the use of deferasirox is acceptable.

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted by WMP have identified a cost utility analysis of the use of deferasirox against DFO in previously untreated patients with the beta thalassaemia in the USA[15]. A Markov model was developed with a time horizon of 50 years. The model focused explicitly on cardiac complications (including mortality) that mainly depended on compliance with therapy (and age), since efficacy in maintaining or reducing LIC was similar between the two therapies. The incremental cost per QALY gained with deferasirox in comparison with DFO was $28,255[15]. There are too many differences in the modelling approaches used and the health care systems considered to draw meaningful comparisons between the published analysis and that presented in the company submission.

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company's submission describes a cost-utility analysis of deferasirox at a dose of 20–30 mg/kg/day compared with DFO at doses of ≥35 mg/kg/day (i.e. the initial doses used in patients with baseline LIC > 7 mg Fe/g dw in the clinical trials). The model considers three patient groups: beta thalassaemia, SCD and MDS. These groups make up the majority of patients requiring ICT in Wales. It is assumed that deferasirox and DFO are equally effective in chelating iron, and differences between the two agents are related only to differences in utility (quality of life), and costs that arise due to the different methods of treatment administration and adverse events[8].

The model has only a one-year time horizon, which would seem inappropriate for modelling a treatment that is life long. In addition, the licensed indications for deferasirox imply that it is only indicated for use in patients with SCD or MDS when DFO is contraindicated or inadequate[1]. However, the model compares deferasirox against DFO in these patients, which precludes assessment of its cost effectiveness in those cases where DFO is not/no longer considered an appropriate treatment option.

8.3.2 Population

The three patient groups considered in the company's submission are the most relevant populations for assessing the cost-effectiveness of deferasirox, but see 8.3.4.

Data on the mean dose of drugs and adverse events from studies 107 (for beta thalassaemia), 109 (for SCD), and US02, US03 and 2409 (for MDS) have been used in the model. Studies 107, 109 and 2409 were multinational studies that included patients from the UK. US02 and US03 were conducted in the US, where the mean body weight of patients was greater than in the multinational studies. Therefore, studies US02 and US03 are used to provide data on the mean dose of deferasirox in patients with MDS, but not the mean body weight (see 8.3.6)[8].

8.3.3 Perspective and time horizon

The model considers direct health-related costs from the perspective of the UK NHS. The analysis did not include any potential Personal Social Services costs. A one year time horizon is used[8]. Patients with transfusion-dependent anaemias require life long ICT. The time horizon would therefore seem inappropriate for this condition.

8.3.4 Comparator

DFO is the current standard treatment for transfusion-dependent iron overload and is used as the comparator for deferasirox in each of the three modelled patient groups. However, the licensed indications for deferasirox suggest it is a first line treatment option only in patients with beta thalassaemia aged ≥6 years. In other patient groups (e.g. SCD, MDS), the licensed indications imply deferasirox is to be used if DFO is contraindicated or as a second line treatment option when DFO is inadequate[1]. The modelling of deferasirox against DFO in the SCD and MDS patient groups therefore does not provide an indication of the cost effectiveness of deferasirox in those cases where DFO is not considered an appropriate treatment option.

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

The model assumes that deferasirox and DFO have equivalent efficacy (as measured by surrogate markers of iron burden such as LIC, serum ferritin, etc.) in each of the modelled patient groups. This is based on data from studies 107 (beta thalassaemia patients), 109 (SCD patients) and 108 (MDS patients) in a subpopulation of patients with baseline LIC ≥7 mg Fe/g dw, as discussed in section 6.1 and 7.2.

Study 108 was a non-comparative study (see section 6.1.2.2). Studies US02, US03 and 2409 provide interim data on patients with MDS that appear generally consistent with the findings of study 108 in terms of effects on serum ferritin levels. It is assumed in the company submission that ICT with deferasirox is equivalent to that with DFO on the basis of indirect comparisons with the results observed in studies in other patient groups[8]. A formal statistical indirect analysis was not performed.

Compliance with treatment is not considered in the model. The company submission presents brief details of a small study that indicated compliance with deferiprone (an oral iron chelating agent that is administered three times a day) was improved compared with DFO[16] and from this suggests that compliance with deferasirox would potentially be improved to an even greater extent compared with DFO (on the basis of deferasirox being a once daily oral treatment)[8]. Additional data provided as commercial in confidence.

8.3.5.2 Adverse events

The model considers the adverse events of abdominal pain, diarrhoea, nausea and rash, as these were found in the trials to occur significantly more frequently in patients treated with deferasirox than with DFO. The probability of experiencing these adverse events has been derived from the pooled one-year data from patients with beta thalassaemia and SCD, and is assumed to be the same in all patient groups. It should be noted that diarrhoea occurred in 17% of beta thalassaemia and SCD patients, and is assumed to last for 2 weeks[8]. However, in patients with rare anaemias (including those with MDS in study 108), diarrhoea is reported to have occurred in 42.2% of patients. The extent to which this adverse event is adequately captured in the model is therefore uncertain but is unlikely to significantly alter the model outputs.

The increases in serum creatinine levels identified in the trials are accounted for in the model by increased serum creatinine monitoring (see 8.3.6). The model has only a one year time horizon and is mainly populated with data from one-year studies. The long term renal and other adverse effects of deferasirox, and the impact these might have on the true cost effectiveness of deferasirox over time, are unknown.

Additional data provided as commercial in confidence.

8.3.5.3 Utility weights

Utility weights associated with the administration regimens have been derived through a time trade off (TTO) exercise involving 120 adult members of the UK general population. Beta thalassaemia was used to describe the need for regular transfusions and ICT, and health states were defined to describe what treatment with subcutaneous and oral ICT involves, which are reported to have been validated by five UK clinicians specialising in the treatment of beta thalassaemia. Mean estimates of utility values were calculated for each treatment. Oral treatment was estimated to be associated with 0.17 greater utility units than subcutaneous treatment when measured using TTO techniques[14]. It is unclear how well balanced the TTO exercise was, as (for instance), a corresponding description for oral therapy to "This treatment has been used effectively and safely by patients for many years [in the case of s/c therapy]" was not included.

For the treatment-related adverse events, estimates of disutility were derived from published economic studies conducted in other conditions (e.g. treatment of parasitic infestations[18] and dyspepsia[19]). The lowest estimates of disutility from these other studies were assumed in this model on the basis that the adverse events were mainly mild and transient in the deferasirox trials. Annual utility decrements of 0.0137 have been assumed for each of abdominal pain, vomiting and diarrhoea[18], and 0.005 for rash[19], which were assumed to be additive in those who experienced more than one of these adverse events[8]. Again, the extent to which these reflect the adverse events experienced by patients receiving ICT is uncertain

8.3.6 Healthcare resource utilisation and cost

8.3.6.1 Drug costs

For the beta thalassaemia population, the mean doses of deferasirox and DFO used in study 107 in patients with baseline LIC > 7 mg Fe/g dw have been assumed (24.54 mg/kg/day and 46.48 mg/kg/day, respectively). These mean drug doses have been multiplied by the mean patient weight in study 107 (reported as 42kg based on all patients in study 107; it is unclear what the mean weight of patients with baseline LIC >

7 mg Fe/g dw was), and costs derived from the British National Formulary (BNF)[6] for deferasirox and DFO have been used. The cost assumed for DFO is based on the Desferal® brand, which costs £4.44 per 500mg vial. A non-proprietary DFO is listed in the current BNF (cost of £4.26 per 500mg vial)[6], which when used in the model increases the base case incremental cost/QALY for deferasirox in MDS patients by almost 30%. No consideration appears to have been given to the rounding of doses and/or potential for DFO vial wastage, which potentially favours DFO in the analyses.

In the modelled SCD population, the mean drug doses and body weight (reported as 52kg) from study 109 have been assumed. The same approach to using drug costs as above has been applied.

In the modelled MDS population, the mean deferasirox dose has been obtained from studies US02, US03 and 2409 (reported as 21 mg/kg/day). As the MDS studies do not contain a DFO arm, the mean DFO dose has been assumed from study 107 (beta thalassaemia patients), with a proportionate decrease applied to reflect the difference in deferasirox doses between studies 107 and the MDS studies (i.e. the mean DFO dose from study 107 has been multiplied by 21.0/25.54). The reliability of this approach is uncertain as only interim data from these studies is available. The mean patient weight for MDS patients has been assumed from study 2409 (71kg), as this study includes patients from the UK and other European countries. Studies US02 and US03 were conducted only in the US, and mean patient body weight in these studies is somewhat greater than in the multinational study 2409[8].

8.3.6.2 Equipment costs

No specific equipment costs are assumed for deferasirox. However, DFO administration requires subcutaneous infusion over 8–12 hours, so requires an infusion pump, plus disposable equipment, etc. The model assumes that 79% of patients use an elastomeric balloon type of infusion device and the remainder use the significantly less expensive battery operated type. This is based on a retrospective chart review study conducted in 29 ICT recipients in four centres in the UK, 2005[20], who administered DFO a mean of 4.5 times per week. This study has also been used to provide other equipment costs, such as needles and other disposable items, etc. These costs have been inflated to 2007 prices. The model is very sensitive to the assumptions on the proportion of patients using each type of infusion device (see 8.3.9).

8.3.6.3 Monitoring costs

Patients treated with deferasirox require increased serum creatinine monitoring compared with patients treated with DFO[3]. In the model, this is assumed to consist of one extra serum creatinine test per month at a cost of £12 each. The Summary of Product Characteristics for deferasirox recommends that serum creatinine monitoring is done weekly in the first month of treatment or following dose adjustment, and monthly thereafter[1]. During study 107, in patients with beta thalassaemia, it is reported that a third of patients required dose adjustment[8]. In addition, monthly tests for proteinuria are recommended, along with liver function tests[1]. The extent to which all additional monitoring requirements and costs for deferasirox are accounted for in the model is therefore uncertain.

8.3.6.4 Adverse events

Abdominal pain is not costed, as this is assumed to be related to the diarrhoea and nausea. Nausea and vomiting is estimated to cost £59, on the basis of a 2004 physician survey related to patients undergoing breast cancer treatment, and has been inflated to £62.85 (2007 prices). Diarrhoea is assumed to be treated for two weeks using codeine phosphate 30mg four times a day, and patients experiencing rash are assumed to be treated with hydrocortisone 0.5% cream (30g tube). These are small contributors to the overall cost estimates, but codeine phosphate is not recommended in children for the treatment of diarrhoea and alternative treatments (e.g. loperamide) may be preferred in other patients. In addition, the duration of diarrhoea is uncertain (see 8.3.5.2). £30 has been added for the costs of a GP visit for each episode of diarrhoea and rash[8].

8.3.7 Discounting

No discounting has been applied to costs or outcomes, as a one year time horizon has been used in the model (see 8.3.3)[8].

8.3.8 Results[8]

The results presented are those reported in the company submission and, given the issues outlined above, are subject to some uncertainty. The 95% credible interval is wide, reported to range from DFO dominated to an incremental cost per QALY of £80,620 for each of the analyses below. However, this appears to be static in the model.

8.3.8.1 Base case analysis: beta thalassaemia population

Deferasirox is associated with lower annual costs (-£1,492) and greater utility (0.177) than DFO. Therefore, deferasirox dominates DFO.

8.3.8.2 Base case analysis: SCD population

Deferasirox is associated with lower annual costs (-£930) and greater utility (0.177) than DFO. Therefore, deferasirox dominates DFO.

8.3.8.3 Base case analysis: MDS population

The incremental cost per QALY gained for deferasirox versus DFO is £7,219 on the basis of additional costs of £1,275, and a gain in utility of 0.177.

8.3.9 Sensitivity analysis[8]

8.3.9.1 One-way sensitivity analyses

One way sensitivity analyses were conducted to assess the impact of varying the mean patient weight and the mean deferasirox and DFO doses by +/-10%:

Deferasirox still dominated DFO in patients with beta thalassaemia and SCD when patient weight was changed by +/-10%. In MDS patients, the incremental cost per QALY ranged from £2,150 to £12,288.

Varying the dose of deferasirox or DFO by +/- 10% produced the results in Table 4:

Table 4. One-way sensitivity analysis on deferasirox and DFO doses[8]:

	Incremental cost per QALY deferasirox v DFO	
	Mean deferasirox dose (+/-10%)	**Mean DFO dose (+/-10%)**
Beta thalassaemia	**[22mg to 27mg]** Deferasirox dominates	**[42mg to 51mg]** Deferasirox dominates
SCD	**[20mg to 24mg]** Deferasirox dominates to £1,850	**[38mg to 47mg]** Deferasirox dominates
MDS	**[19mg to 24mg]** Deferasirox dominates to £22,010	**[36mg to 44mg]** £2,007 to £12,431

No other one-way sensitivity analyses are presented, such as effect of disutility associated with adverse events (see 8.3.5.3).

8.3.9.2 Two-way sensitivity analysis

Two-way sensitivity analysis was conducted by varying the utility difference (excluding the influence of adverse events, 0.180) between the lower and upper limits of the bootstrap-derived 95% confidence interval (0.147 to 0.212) and percentage use of the balloon infuser device (100% to 60%). This showed that the model was sensitive to the assumptions on percentage use of the balloon infuser device. When balloon device was used in 100% of patients, deferasirox dominated DFO in all three patient populations and all tested utility value differences, but when the balloon device was used in 60% of patients, the incremental cost effectiveness ratios changed:

Beta thalassaemia: the incremental cost per QALY gained ranged from £340 to £494 when the utility value differences were varied between 0.212 and 0.147.

SCD: the incremental cost per QALY gained ranged from £3,035 to £4,409 when the utility value differences were varied between 0.212 and 0.147.

MDS: the incremental cost per QALY gained ranged from £13,603 to £19,760 when the utility value differences were varied between 0.212 and 0.147.

8.3.9.2 Probabilistic sensitivity analysis

Cost-effectiveness acceptability curves have been generated by sampling the parameters of the model in 2,000 simulations. Few details are provided beyond the result graphs. The approximate probabilities of deferasirox being cost effective at willingness to pay thresholds of £20,000 or £30,000 per QALY are presented in Table 5:

Table 5. Probability of deferasirox being cost effective[8]

	Approx. probability cost effective at willingness to pay:	
	£20,000 per QALY	£30,000 per QALY
Beta thalassaemia	83%	88%
SCD	82%	87%
MDS	64%	75%

The generated curves are a function of the model inputs. This probabilistic analysis does not address the issues outlined above in relation to the DFO drug costs, serum creatinine monitoring, one year time horizon, etc.

8.4 Review of evidence on budget impact:[8]

8.4.1 Description and critique of the company's submission

The company's submission considers the budget impact of the use of deferasirox over DFO from the perspective of NHS Wales. The model assumes that all patients estimated to be currently treated with DFO would be eligible for treatment with deferasirox. However, the licensed indications for deferasirox imply it is a first line treatment option only in patients with beta thalassaemia aged $\geq$ 6 years. In other patient groups, deferasirox is licensed for use when DFO is inadequate or contraindicated[1]. The budget impact model does not provide any data on the extent to which deferasirox may be used as second line therapy or when DFO is not considered an appropriate treatment option.

8.4.2 Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon.

8.4.3 Data sources

8.4.3.1 Incident cases

The incidences of beta thalassaemia and SCD have been assumed to be the same as in Scotland, on the basis that the demographic make up is similar in Wales. The incidence for beta thalassaemia has been assumed to be 0.9 per 100,000 population/year and for SCD 3.1 per 100,000 population per year (the HbSS variant, which it is claimed is the SCD group most likely to receive transfusions). No details or references are provided to support these assumptions.

For MDS, the overall incidence has been estimated as 4 per 100,000 population[12]. Based on the population of Wales (2,958,600), a total annual incidence of 118 patients is calculated. Based on a retrospective study of prognostic factors in Italian patients with MDS[21], 34% of patients (40) are expected to be low risk and 39% (46) INT-1 risk for conversion to acute myeloid leukaemia, giving a total number of patients in Wales of 86 patients per year with MDS eligible for transfusion therapy.

8.4.3.2 Prevalent cases

The prevalence of beta thalassaemia and SCD has been derived from a study of the prevalence of haemoglobinopathies in Wales. Using physician surveys and data from the Patient Episode in Wales Database, prevalence estimates are reported to have ranged from 60 patients to 148 patients[22]. The model has assumed the upper estimate[8],

and it is suggested that 74 patients have beta thalassaemia and 74 patients have SCD in Wales[22].

The prevalence of MDS has been estimated from the assumed MDS incidence data above, by multiplying this by estimates of survival. Survival curves for patients with low risk and INT-1 risk MDS have reportedly been extrapolated to 25 years from data in a published study of prognostic factors in Italian MDS patients[21]. This is reported to have been done by assuming a constant mortality risk from 10 years to 25 years[8]. Mean survival times for the low and INT-1 risk groups are stated to be 6.2 years and 4.66 years, respectively. The prevalence of MDS in Wales is therefore estimated to be (40 patients x 6.2 years) + (46 patients x 4.66 years) = 462 patients.

The total number of beta thalassaemia, SCD and MDS patients is therefore estimated as 610 (74+74+462). The company submission states that this may increase by one patient per year over the next five years so that in 2012 there may be 614 patients at risk of iron overload, although no data to support this assumption are provided.

A company-sponsored survey of 10 UK specialists has been conducted to determine the proportions of patients who are treated with ICT. No data are provided beyond the results, which are reported to indicate that ICT therapy is received by 97% of beta thalassaemia patients, 20% of HbSS SCD patients and 12% of MDS patients. This would suggest that, of the 610 patients estimated to be at risk of transfusion-dependent iron overload in Wales, 142 are currently receiving ICT. The company submission states that these 142 patients would potentially be eligible for treatment with deferasirox. However, this would not appear to be consistent with the licensed indications for deferasirox, which suggest use in SCD and MDS would be in those with contra-indications to DFO or those in who DFO is inadequate (i.e. second line use)[1]. For simplicity, the model assumes that the number of patients eligible for ICT over the next five years remains constant at 142.

8.4.3.3 Rates of adoption

The uptake of deferasirox is unknown but has been assumed in the model to be 30% of all patients eligible for ICT in 2008, rising by an absolute 10% each year to 70% in 2012. The company submission states that these estimates of uptake take into account a possible increase in the proportion of patients with MDS who receive ICT (on the basis that deferasirox is more convenient and associated with greater quality of life than DFO). However, the rates of uptake are applied equally to the figures quoted for each of beta thalassaemia, SCD and MDS.

The model suggests that 43 patients would receive deferasirox in 2008, rising to 99 patients in 2012. These estimates appear not to be guided by the licensed indications for deferasirox.

8.4.3.4 Costs and resource use

In calculating the direct drug intervention costs, the acquisition costs of deferasirox and DFO have been assumed from the cost-effectiveness model. The non-drug costs have also been assumed from the cost-effectiveness model. These assume that deferasirox is associated with 12 additional serum creatinine tests per year and that 79% of patients receiving DFO use an elastomeric balloon type of infusion device. The infusion device

type is a significant driver of the results of the cost effectiveness model, as it is a significant component of the non-drug costs of DFO treatment. A change in the proportion of patients using the balloon or battery infusion device could have a significant impact on the budget impact model. No sensitivity analyses have been conducted around this or any other assumptions.

8.4.4 Results

The figures below relate to those stated in the company submission. If used within its licensed indications, the number of patients eligible for treatment with deferasirox could be lower than is assumed in this model.

Table 6. Budget impact estimates 2008 to 1012

	2008	**2009**	**2010**	**2011**	**2012**
Estimated No. patients deferasirox	43	57	71	85	99
Additional cost of deferasirox over DFO (£)	320,789	424,144	529,704	633,059	738,619
Savings in non-drug costs with Deferasirox over DFO (£)	335,615	444,885	554,155	663,425	772,695
Net cost impact (£)	**-14,826**	**-20,741**	**-24,451**	**-30,366**	**-34,076**

8.4.5 Sensitivity analysis

No sensitivity analysis has been conducted.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Guidance on the treatment of transfusion dependent anaemias includes:

  Bowen D, Culligan D, Jowitt S, et al. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003; 120(2):187–200.

  United Kingdom Thalassaemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. 1-90. 2005.

- A Health Technology Assessment of deferasirox is in process, with results expected to be published in December 2008 (see http://www.hta.ac.uk/project/1632.asp).

- Treatment with deferasirox should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions[1]. The specialist nature of the underlying transfusion-dependent anaemias would suggest that deferasirox is unsuitable for shared care.

9.2 Previous AWMSG/NICE advice:

None applicable.

9.3 Ongoing studies[8]:
Studies US02, US03 and 2409 are ongoing studies from which interim data is available for patients with MDS – commercial in confidence data provided by the company.

Study 2201 (n-210) is a phase II, randomised, active control (DFO) trial to examine the long-term safety and efficacy of deferasirox in patients with SCD and iron overload from repeated blood transfusions. Study completion is expected in February 2008.

Study MDS0306 (n=158) is an Italian multicentre, phase III, single arm, open label trial to assess the safety and efficacy of deferasirox in patients with MDS with post-transfusional haemosiderosis over one year. Study completion is expected in Q4 2008.

Study DE03 (n=120) is a phase IV, single arm, open label trial that is being conducted to evaluate the efficacy and safety of deferasirox in patients diagnosed with Low and INT-1 risk MDS, with transfusion-dependent iron overload, over one year using serum ferritin monitoring. Study completion is expected in Q4 2008.

Several extension studies (107E1 [n=507], 108E1 [n=142], 106E1 [n=39], 2402E1 [n=250] and 109E1 [n=154]) are providing additional long-term efficacy and safety data in all patients with transfusional haemosiderosis. Studies 2203 (phase III, open label, expanded access trial, n=1396), 2411 (US phase IV observational study in 200 children aged 2 to < 6 years) and US04 (US phase II trial to evaluate cardiac T2* in 30 beta thalassaemia patients) are also ongoing. No details are provided in the company submission of when these studies will report final results.

9.4 Patient Interest Group information
A patient interest group submission by the UK Thalassaemia Society (UKTS) was provided to AWMSG members.

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Appendix 1

Table 1A. Success rates based on LIC in the primary efficacy analysis of study 107[3]

	Deferasirox N=276	**DFO N=277**
Primary efficacy per protocol population	**n=276**	**n=277**
Success rate (n [%])	146 (52.9)	184 (66.4)
95% CI	[47.0 to 58.8]	[60.9 to 72.0]
Absolute percentage difference (deferasirox-DFO) and 95% CI	**-13.5% [-21.6 to -5.4]**	
LIC < 7 mg Fe/g dw*	**n=85**	**n=87**
Success rate (n [%])	34 (40.0)	72 (82.8)
95% CI	[29.6 to 50.4]	[74.8 to 90.7]
Absolute percentage difference (deferasirox-DFO) and 95% CI	-42.8% [-55.9 to -29.7]	
LIC ≥ 7 mg Fe/g dw	**n=191**	**n=190**
Success rate (n [%])	112 (58.6)	112 (58.9)
95% CI	[51.7 to 65.6]	[52.0 to 65.9]
Absolute percentage difference (deferasirox-DFO) and 95% CI	**-0.3% [-10.2 to 9.6]**	

Table 2A. Absolute changes in LIC, serum ferritin and iron balance in the secondary efficacy per protocol population of study 107[3,8]

LIC in mg Fe/g dw	**Median dose mg/kg/day**		**Iron burden at EOS (based on available values)**	**n**	**Mean ± SD deferasirox**	**n**	**Mean ± SD DFO**
	Deferasirox	**DFO**					
Secondary efficacy per protocol population	-	-	Change in LIC (mg Fe/g dw)	268	-2.4 ± 8.2	273	-2.9 ± 5.4
			Ratio iron excretion/ intake	224	1.21 ± 0.745	230	1.21 ± 0.476
LIC ≤ 3	5	30	Change in serum ferritin (ng/ml)	15	+ 1189 ± 700	13	+ 211 ± 459
			Change in LIC (mg Fe/g dw)	15	+ 4.8 ± 3.77	13	+ 0.5 ± 1.11
			Ratio iron excretion/ intake	15	0.58 ± 0.328	13	0.95 ± 0.101
LIC > 3-7	10	35	Change in serum ferritin (ng/ml)	73	+ 833 ± 817	77	+ 32 ± 585
			Change in LIC (mg Fe/g dw)	68	+ 3.8 ± 3.85	75	0.0 ± 2.36
			Ratio iron excretion/ intake	68	0.67 ± 0.365	75	0.98 ± 0.217
LIC > 7-14	20	41	Change in serum ferritin (ng/ml)	80	-36 ± 721	89	-364 ± 614
			Change in LIC (mg Fe/g dw)	77	-0.4 ± 4.70	87	-1.9 ± 2.93
			Ratio iron excretion/ intake	77	1.02 ± 0.398	87	1.13 ± 0.241
LIC > 14	30	51	Change in serum ferritin (ng/ml)	115	-926 ± 1416	101	-1003 ± 1428
			Change in LIC (mg Fe/g dw)	108	-8.9 ± 8.07	98	-6.4 ± 6.93
			Ratio iron excretion/ intake	108	1.67 ± 0.716	98	1.44 ± 0.596

Table 3A. Success rates in the different anaemia-type groups (per protocol populations) from study 108[8]

	MDS N=39	**DBA N=27**	**Other anaemias N=19**	**β-thal N=80**
Biopsy or SQUID				
Success rate (n [%]) 95% CI p-value (1-sided, alpha=2.5%)	22 (56.4) [40.8 to 72.0]	14 (51.9) [33.0 to 70.7]	12 (63.2) [41.5 to 84.8]	45 (56.3) [45.4 to 67.1]
LIC < 7 mg Fe/g dw* Success rate (n [%]) 95% CI	**n=9** 6 (66.7) [29.9 to 92.5]	**n=4** 2 (50) [6.8 to 93.2]	**-** - -	**n=10** 2 (20.0) [2.5 to 55.6]
LIC ≥ 7 mg Fe/g dw Success rate (n [%]) 95% CI p-value (1-sided, alpha=2.5%)	**n=30** 16 (53.3) [35.5 to 71.2]	**n=23** 12 (52.2) [31.8 to 72.6]	**n=19** 12 (63.2) [41.5 to 84.8]	**n=70** 43 (61.4) [50.0 to 72.8]

* Patients with a LIC < 7 mg Fe/g dw received sub-optimal doses of 5 to 10 mg/kg/day of deferasirox. 5 mg/kg/day is an unlicensed dose and 10 mg/kg/day is only recommended under particular circumstances.