Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

# Re-Submission

## deferasirox 125mg, 250mg, 500mg dispersible tablets (Exjade®)

SMC No. (347/07)

## Novartis Pharmaceuticals UK Limited

09 December 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a resubmission considered under the ultra-orphan process

**deferasirox (Exjade®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** Treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate, in adult and paediatric patients aged 2 years and older with rare acquired or inherited anaemias.

The current advice relates only to use in the myelodysplastic syndrome (MDS) population.

**SMC restriction:** use in patients with MDS with an International Prognostic Scoring System (IPSS) score of low or intermediate -1 risk.

Plasma ferritin levels were statistically significantly reduced from baseline to end of study in two phase II/III open-label, single-arm studies of patients with MDS with an IPSS score of low or intermediate -1 risk.

SMC has previously accepted deferasirox for restricted use for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. This advice remains valid.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

Published 16 January 2017

## Indication

Treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate, in adult and paediatric patients aged 2 years and older with rare acquired or inherited anaemias.

The current submission relates only to use in the myelodysplastic syndrome (MDS) population.

## Dosing Information

The recommended initial dose of deferasirox dispersible tablets is 20mg/kg (body weight), taken once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day.

An initial daily dose of 30mg/kg may be considered for patients who require reduction of elevated body iron levels and who are also receiving more than 14mL/kg/month of packed red blood cells (approximately >4 units/month for an adult). An initial daily dose of 10mg/kg may be considered for patients who do not require reduction of body iron levels and who are also receiving less than 7mL/kg/month of packed red blood cells (approximately <2 units/month for an adult). The patient's response must be monitored and a dose increase should be considered if sufficient efficacy is not obtained.

Treatment with deferasirox should be initiated and maintained by physicians experienced in the treatment of chronic iron overload.

## Product availability date

September 2006

Deferasirox was designated an orphan medicine for the treatment of chronic iron overload requiring chelation therapy by the European Medicines Agency (EMA) on 13 March 2002.[1]

Deferasirox meets SMC ultra-orphan criteria.

## Background

Deferasirox is an orally active iron chelator for the treatment of chronic iron overload due to blood transfusions.[2] In 2007, SMC accepted deferasirox for restricted use for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It was not recommended for patients with myelodysplastic syndrome (MDS).

The current resubmission concerns use of deferasirox for the treatment of chronic iron overload in patients with MDS requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate, The company has requested that SMC considers this submission positioned for use in patients with an International Prognostic Scoring System (IPSS) score of low or intermediate-1 (Int-1) risk. Deferoxamine is referred to as desferrioxamine hereafter.

Deferasirox for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

## Nature of condition

MDS includes a range of malignant haematopoietic disorders which are characterised by impaired haematopoiesis and increased risk of development of AML. Around half of patients will develop severe anaemia (haemoglobin <10g/dL), and requirement for regular transfusions has been linked with increased risk of death and shorter leukaemia-free survival. MDS generally occurs in older patients with an incidence greater than 30 per 100,000/year in patients over the age of 70 years. Management is largely defined by the IPSS scoring system where 'low risk' includes patients with IPSS of low or Int-1 risk. The median overall survival without treatment is 5.7 years in patients with IPSS low risk and 3.5 years in IPSS Int-1 risk. Iron chelation therapy is not recommended routinely in patients with MDS and transfusional iron overload, but should be considered in patients with a very good prognosis. Deferasirox is designated an orphan medicine for the treatment of chronic iron overload requiring chelation therapy and meets SMC ultra-orphan criteria for the indication under review.[1,3,4,5]

A patient and clinician engagement (PACE) meeting was held to consider the added value of deferasirox in the context of treatments currently available in NHS Scotland. At the PACE meeting, attention was drawn to a clear unmet need for a better tolerated iron chelation therapy for this rare disease. Currently the only available chelation therapy for patients with MDS is desferrioxamine. Due to its poor oral bioavailability and short half-life, administration is usually by subcutaneous infusion over a period of 8–12 hours for 5-7 days each week. As patients are generally older, many are unable to tolerate this intense long term regimen. Additionally, patients with sight or dexterity issues may be unsuitable for desferrioxamine by infusion.

## Impact of new technology

**Summary of evidence on comparative efficacy**

The submitting company presented clinical data from several observational and single-arm studies. The studies considered most relevant to the positioning proposed by the company are two phase II/III single-arm studies (US03 and GIMEMA) and a prospective observational study (MORE).[4,6,7,8,9]

The open-label, single-arm phase II/III studies were undertaken in patients with IPSS low or Int-1 risk MDS and who had received at least 20 units of red blood cells and had a serum ferritin greater than 1,000 micrograms/L at screening. In the US03 study, 173 patients received open-label deferasirox dispersible tablets at a starting dose of 20mg/kg/day which could be increased by 10mg/kg/day up to 40mg/kg/day, based on responses in serum ferritin and treatment tolerance; patients were treated for up to three years. In the GIMEMA study, 152 patients received open-label deferasirox dispersible tablets at a starting dose of 10mg/kg/day to 30mg/kg/day, for one year. Both studies assessed safety as the primary outcome.[6,7]

In the US03 study, around half of patients were naive to iron chelation therapy. From a baseline value of 2,772 micrograms/L, serum ferritin level decreased by 25% (median, 561 micrograms/L) at one year (in 91 actively treated patients), $p<0.001$. Serum ferritin levels decreased from baseline by 36% at year two (in 49 actively treated patients) and 37% at year three (in 33 actively treated patients). Patients received red blood cell transfusions when clinically indicated and the mean transfusion rate over 12 months was 4.1 red blood cell units per month. A post hoc analysis of haematological responses using International

Working Group (IWG) 2006 criteria was undertaken during the first year. IWG 2006 criteria define erythroid response (assessed in patients with pre-treatment haemoglobin level <11g/dL) as an increase in haemoglobin of ≥1.5g/dL and reduction of ≥4 red blood cell transfusions over eight weeks compared with the pre-treatment transfusion number in previous eight weeks. A platelet response (assessed in patients with pre-treatment level $<100x10^9$/L) is defined as an absolute increase of $\geq 30x10^9$/L (pre-treatment level $>20x10^9$/L) or $>20x10^9$/L (pre-treatment level $<20x10^9$/L) and by at least 100%. A neutrophil response (assessed in patients with pre-treatment level $<1.0x10^9$/L) is defined as at least 100% increase and an absolute increase $>0.5x10^9$/L.[9] Erythroid response occurred in 15% (26/173) of patients, platelet response in 22% (17/77) of patients and neutrophil response in 15% (8/52) of patients. These analyses include patients who were on other haematological modifying treatments. The median time to haematologic response was 169 days.[6]

In GIMEMA, from baseline value of 1,966 micrograms/L, the decrease in median serum ferritin level was 490 micrograms/L at one year, $p<0.001$. Using IWG 2006 criteria (and excluding patients on other haematological modifying treatments), a platelet response was achieved in 15% (19/125) of patients and a neutrophil response in 3.2% (4/125) of patients. Erythroid response was defined as achievement of transfusion independence and occurred in 11% (16/145) of patients at 12 months.[7] Quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) at baseline and then every three months up to month 12. There were no statistically significant changes from baseline to month 12 for global health status/QoL, physical functioning, fatigue, constipation, diarrhoea, and nausea and vomiting in the primary longitudinal analysis; this was also the case for the exploratory analysis of the remaining scales/items.[7,8]

MORE was a prospective, five-year observational study in lower-risk adult patients with MDS and transfusional iron overload (defined as in phase II studies), where patients were followed up every six months for up to 60 months or death. Patients were analysed at each time point according to their chelation status: 'no iron chelation therapy' and 'iron chelation therapy', where the latter group included patients who had received any iron chelation. A subgroup analysis was planned for patients who had received ≥ six months of iron chelation therapy as this duration was considered to be a sufficient treatment period. At 24 months, 263 patients had received iron chelation therapy, with the majority of patients receiving deferasirox. At 60 months, 271 patients had received iron chelation therapy; deferasirox was received by 69% (187/271) of patients, desferrioxamine and deferasirox by 15% (40/271) of patients and desferrioxamine by 12% (32/271) of patients (and was unknown in 12 patients). The proportion of patients who remained on treatment at 60 months was 10%; 90% of patients had discontinued treatment (67% due to death, 11% were lost to follow-up and 4.3% for other reasons). The number of patients who had completed the study was 46 (7.7%).[4,9]

Overall survival was the key outcome and was calculated from the date of MDS diagnosis. Results are reported in table 1 for the 24- and 60-month time points and also for cardiovascular and endocrine subgroups at 60 months.[4,9]

**Table 1; overall survival (from time of MDS diagnosis) from the MORE study** [4,9]

| | no iron chelation group | iron chelation group | ≥ six months iron chelated subgroup |
|---|---|---|---|
| **At 24 months** | | | |
| Overall survival, months | 52.2 | 99.3 | 104.4 |
| Deaths % (n/N) | 51% (171/337) | 41% (107/263) | 37% (70/191) |
| **At 60 months** | | | |
| Overall survival, months | 47.8 | 88.0 | 100.0 |
| Deaths % (n/N) | 73% (239/328) | 59% (161/271) | 57% (115/202) |
| **At 60 months in cardiovascular and endocrine co-morbidity subgroups** | | | |
| Cardiovascular co-morbidity, n | n=286 | n=199 | n=142 |
| Overall survival, months | 43.4 | 67.7 | 72.6 |
| Endocrine co-morbidity, n | n=166 | n=122 | n=88 |
| Overall survival, months | 44.6 | 75.0 | 81.8 |

The submitting company provided an analysis of overall survival (from initiation of iron chelation therapy) using individual patient data (IPD) which was used to inform the economic model.

At 24 months, median ferritin levels were generally unchanged from baseline in both the iron chelation and no iron chelation groups.[4] At 60 months, the proportion of patients who progressed to acute myeloid leukaemia (AML) was 10% (34/328) in the no iron chelation group and 6.3% (17/271) in the iron chelation group (and 6.9% [14/202] in the subgroup of patients who had received ≥ six months of iron chelation). Median time from MDS diagnosis to progression to AML was 46.4 months in the no iron chelation group and 72.1 months in the iron chelation group (and 78.8 months in the subgroup of patients who had received ≥ six months of iron chelation).[9]

A meta-analysis of eight observational studies (including the MORE study) investigated associations between iron chelation therapy (but not specific treatments) and survival in patients with MDS. Results indicated that the likelihood of longer median overall survival was increased in patients on iron chelation therapy compared with those not on iron chelation therapies; odds ratio 1.98 (95% CI: 1.58 to 2.49) and mean difference in overall survival between the groups was 61 months.[11]

A retrospective, two-year observational 'real-world' study was conducted in 118 patients with MDS (no restriction on risk severity) who were transfusion dependent and treated with deferasirox (starting dose 10 to 20mg/kg) for 24 months. The reduction in serum ferritin (from a baseline value of 1,790 micrograms/L) was statistically significant from month six, onwards, and at 24 months, median serum ferritin level was 1,140 micrograms/L. At baseline the transfusion requirement was 2.0 units/month and at month 24 was 2.9 units/month. In an analysis which excluded 32 patients on concurrent azacitidine or lenalidomide the proportion of patients who became transfusion independent was 7.1% (6/85).[12]

*Other data were also assessed but remain commercially confidential.**

**Summary of evidence on comparative safety**
There are no comparative safety data.

In the US03 study, around a quarter of patients discontinued from the study due to adverse events. The most common moderate to severe adverse events were gastrointestinal (diarrhoea, nausea and vomiting), dyspnoea, fatigue, and blood creatinine increase. The proportion of patients who discontinued from the study due to increases in serum creatinine was 10%. Serious renal adverse events, and renal adverse events that led to study drug

discontinuation, occurred in higher proportions of patients who had abnormal baseline serum creatinine values (8.3% and 4.7%) compared with patients with normal values (6% and 0.7%).[6]

In the GIMEMA study, around 18% of patients discontinued from the study due to adverse events. The primary endpoint was treatment-related adverse events (≥ grade 3) which occurred in 7.2% (11/152) of patients (all were grade 3). These included diarrhoea (three events) and one event each for abdominal pain, melena, vomiting, face oedema, cholecystitis, hypertransaminasaemia, anorexia, decreased appetite, renal failure and rash. Median creatinine values increased from a baseline value of 0.87mg/dL to 0.98mg/dL at the end of study.[7]

The European Medicines Agency questioned the preventability, reversibility and long-term consequences of deferasirox effect on modification of renal function, from the clinical evidence submitted for regulatory approval. Furthermore, it noted that no effective measure was identified to reverse the impaired renal function - interrupting treatment did not completely have the desired effect.[13]

**Summary of clinical effectiveness issues**

The submitting company has requested that SMC considers deferasirox for the treatment of chronic iron overload in patients with MDS, positioned for use in patients with an IPSS score of low or Int-1 risk. It considers that desferrioxamine is the key comparator. Desferrioxamine is the treatment of choice when iron chelation therapy is indicated and UK guidance recommends deferasirox for patients intolerant of desferrioxamine.[3] Deferasirox is indicated when desferrioxamine therapy is contraindicated or inadequate. The company stated that patients with an inadequate response (which may be defined as failure to lower serum ferritin levels to <1,000 micrograms/L or to alleviate vital organs) may continue on desferrioxamine treatment, rather than the alternative of no treatment. However, clinical experts consulted by SMC noted that compliance with desferrioxamine is poor, with some patients declining treatment. They considered there is unmet need in terms of an oral iron chelation treatment for patients with MDS.

There are no controlled, comparative efficacy or safety data for deferasirox versus desferrioxamine or no treatment. In two single-arm, open-label phase II/III studies in patients with lower-risk MDS, there were statistically significant decreases from baseline in median serum ferritin levels. At baseline patients were heavily transfused (median 37 to 41 units) and median ferritin levels were generally higher than 2,000 micrograms/L.[6,7] However, patients are required to have a contraindication or inadequate response to desferrioxamine to be eligible for deferasirox and the inclusion criteria of the studies did not specify this. The proportion of patients who discontinued from the studies overall was high, with 18% to 25% discontinuing due to adverse events. The elderly/frail study population, with poor motivation with regards to their disease and poor compliance, was proposed as a reason for the high discontinuation rates.[6,7] QoL was generally stable in patients treated with deferasirox for up to one year in GIMEMA. However, due to the design of the studies, limited conclusions can be drawn regarding efficacy of deferasirox and its impact on QoL.[8]

In the non-randomised, observational study (MORE), 69% of patients in the iron chelation group (at the 60-month analysis) received deferasirox. However, information on doses administered was not available and an analysis of individual treatments was not performed. Patients who received iron chelation (median duration of 19 months) had significantly longer overall survival and time to progression to AML (measured from time of MDS diagnosis) compared with patients who did not receive iron chelation. However, causation cannot be established from observational data alone. There were variations in the time from diagnosis, duration of chelation and impact on patient clinical status on the decision to chelate. Use of concomitant MDS medicines in patients who received iron chelation therapy was numerically

higher than in patients who did not receive iron chelation therapy, which may have contributed to improved overall survival. In this study, there was little change in ferritin levels, unlike the phase II/III studies. This may be due to the different intensities and duration of chelation in a registry design study compared with a clinical study.[4,9] The analysis of overall survival and progression to AML using IPD, used in the economic model, has limitations including those relating to observational data and also no assessment of individual iron chelation treatments.

The uncontrolled study design of the retrospective observational 'real-world' study that reported six patients became transfusion independent means that no conclusions can be drawn in terms of whether treatment with deferasirox can result in transfusion independence.[11] Furthermore, clinical experts consulted by SMC did not consider iron chelation therapy could have such an effect on the course of MDS.

The availability of an oral treatment option may provide benefits to patients and the service compared with desferrioxamine, the current treatment recommended in guidelines, which requires intramuscular or subcutaneous administration five to seven days per week. Treatment with deferasirox and desferrioxamine requires monitoring of serum ferritin levels to guide dose adjustment. Furthermore, renal function should be closely monitored before and during treatment with deferasirox.[2,14,15] Clinical experts consulted by SMC also noted that patients being treated with deferasirox require careful monitoring. They considered that deferasirox is a therapeutic advancement due to its oral administration and improvement in quality of life. They reported that use would be as per licensed indication, in patients who are intolerant of or have contraindications to desferrioxamine, where currently there are no other treatments available.

At the PACE meeting, it was said that transfusion requirements appear to decrease in some MDS patient treated with deferasirox. Additionally, the use of an oral treatment may reduce risk of infection as patients no longer need to use needles.

## Patient and clinician engagement (PACE)

A PACE meeting with patient group and clinical specialist representation was held to consider the added value of deferasirox, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Around half of patients with MDS will develop severe anaemia and the resultant need for regular transfusions. The associated iron overload can cause iron accumulation in vital organs causing potentially life threatening problems such as liver, heart and renal dysfunction. Full compliance with chelation therapy is essential to minimise the impact of iron overload.
- Deferasirox is the only chelation treatment option available for those low to intermediate risk MDS patients who cannot tolerate administration of the desferrioxamine subcutaneous infusion or where this treatment is contra-indicated. It is of particular benefit for patients with sight or dexterity issues or those with a needle phobia.
- Existing chelation treatment involves subcutaneous infusion administered 5-7 days per week. Patients usually use the pump overnight or wear it underneath clothes for eight hours during the day, which may cause pain and discomfort. As such, current treatment is generally associated with an inferior quality of life for the patients.
- PACE participants highlighted their experience that compliance with the oral treatment is greater than that seen with the infusion and consequently deferasirox is a more effective chelation therapy option.

- Deferasirox offers a vastly improved quality of life for patients with MDS and their families/carers by reducing the physical, psychological and emotional burden associated with desferrioxamine infusion therapy.

**Additional Patient and Carer Involvement**
We received a joint submission from Leukaemia CARE and MDS UK Patient Support Group, and a further submission from UK Thalassaemia Society which are all registered charities. Leukaemia CARE has received 10.6% pharmaceutical company funding in the past two years, including from the submitting company. MDS UK Patient Support Group has received 29% pharmaceutical company funding in the past two years, including from the submitting company. UK Thalassaemia Society has received 17.5% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Leukaemia CARE, UK Thalassaemia Society and MDS UK Patient Support Group participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement.

## Value for money

The company submitted a cost-utility analysis comparing deferasirox to desferrioxamine for patients MDS with an IPSS score of low or Int-1 risk for the treatment of chronic iron overload due to blood transfusions when desferrioxamine therapy is contraindicated or inadequate. Based on SMC clinical expert responses, the comparator appears to be appropriate (despite the license indicating that deferasirox should be used when desferrioxamine therapy is inadequate, as some patients are likely to stay on desferrioxamine treatment rather than no treatment). However, clinical experts also reported that some patients may decline desferrioxamine treatment and receive no treatment.

A state transition (Markov) model was submitted, which contained five health states ie transfusion-dependent chelated, transfusion-dependent non-chelated, transfusion-independent MDS, AML and death. Patients progressed through the model according transition probabilities. The time horizon in the analysis was 15 years.

The clinical data used in the economics were taken from published literature and the MORE registry, a 5-year observational study, which collected outcome data according to chelation status. The primary outcome measure was overall survival. Based on the MORE registry and using an unpublished IPD analysis, patients receiving chelation therapy achieved a significant difference in overall survival (calculated from time of chelation) versus patients that did not receive iron chelation therapy. Within the economic model, non-AML survival was estimated by fitting a Cox proportional hazards model to the individual patient data. In relation to progression, the probability of transitioning to AML was taken from IPD (MORE registry). The company assumed equal efficacy in terms of chelation between treatments. However, the published retrospective, observational 'real-world' study (described previously) which included transfusion-dependent patients with MDS, was used to derive the probability of patients transitioning into the transfusion-independent health state (whereby patients were assumed to no longer require chronic blood transfusions or receive iron chelation therapy). Based on this study, 7.1% of patients treated with deferasirox were assumed to become transfusion-independent. It is important to note that in the economic model patients receiving desferrioxamine were not capable of becoming transfusion-independent.

Health state utility values were derived from a number of UK literature sources. The utility values for the treatment chelation health states were derived from a UK published study which elicited values from the general UK population using the time trade-off method. The

patients within this study included children and adults with beta thalassaemia, sickle cell disease and MDS. The following health state values were reported:

| Health state | Utility value |
|---|---|
| Transfusion-independence | 0.85 |
| Transfusion-dependence (with deferasirox chelation) | 0.84 |
| Transfusion-dependence (with desferrioxamine chelation) | 0.66 |
| Transfusion-dependence (no chelation) | 0.84 |
| AML | 0.257 |

Drug acquisition costs were included in the analysis and were based on a patient weight of 77.6kg (based on a 2014 Scottish health survey). The cost associated with desferrioxamine was based on a weighted average of desferrioxamine and Desferal®, whereby the weighted usage was based on company UK pack dispensing data. Deferasirox is an oral medication, therefore no administration costs were included. Administration costs associated with blood transfusions were included in the analysis ie red blood cell unit, haematology day case, blood test, haematology nurse time costs. In the analysis the company assumed that 79% of patients receiving desferrioxamine would use the balloon infuser (annual cost £6,763), whereas 21% would use the pump infuser (annual cost per patient £161). No treatment-specific adverse event costs were included, although the model did include the cost associated with iron overload ie cardiac, diabetes and hepatic costs.

In the base case analysis, deferasirox was considered to dominate desferrioxamine ie was cheaper and more effective. Compared to desferrioxamine, deferasirox resulted in savings of -£6,783 and a QALY gain of 0.58. Although deferasirox was associated with a relatively large incremental drug cost (£27,890) compared to desferrioxamine, this was offset by the lack of iron chelation therapy equipment costs; these were £28,847 for desferrioxamine. In addition, deferasirox resulted in fewer transfusion-related costs, treatment-related monitoring costs and complication costs.

In terms of the QALY gain, this was driven by the difference in quality of life between deferasirox and desferrioxamine chelation health states and the time spent in each health state. Over the duration of the model, patients on deferasirox spent 4.98 months in the transfusion-independent health state and accrued 0.353 QALYs compared to 0 months and 0 QALYs for desferrioxamine patients ie patients on deferasirox did not become transfusion-independent.

The company has provided one-way, scenario and probabilistic sensitivity analysis. According to the scenario analysis, the results most sensitive to variation were as follows.

| Parameter | Variation | Incremental cost-effectiveness ratio (ICER) |
|---|---|---|
| Compliance rate | 50% discontinue with desferrioxamine | £21,569 |
| Desferrioxamine equipment utilisation | 100% use the infusion pump | £28,791 |
| Dosing assumption | Deferasirox (30mg/kg) | £30,891 |

There were a number of weaknesses in the analysis:

- There are no direct head-to-head studies comparing the efficacy and safety of deferasirox to desferrioxamine. The MORE registry is a prospective observational study which compares the impact of iron chelation therapy on overall survival compared to no iron chelation therapy. As such, the comparative efficacy of deferasirox versus desferrioxamine remains uncertain.
- The model includes a health state (transfusion-independence) which does not appear to be appropriate and may bias the analysis. Although treatments are considered to have equal efficacy in terms of chelation, the company assumes that only patients receiving deferasirox can transition into this health state, which slows progression to AML and keeps patients in a relatively high quality of life. Based on SMC expert responses, iron chelation therapy (regardless of treatment) is not likely to impact the transfusion status of a patient. Therefore, the inclusion of a transfusion independence health state does not appear to be appropriate. The company provided additional analysis whereby 0% of patients receiving deferasirox are assumed to transition into this health state. Based on this analysis, deferasirox resulted in an ICER of £14,127 compared to desferrioxamine.
- A large proportion of the QALY gain is derived from the difference in utility between the deferasirox and desferrioxamine chelated health states. There were a number of concerns surrounding the literature source used to estimate these values which used vignettes describing the two health states from the perspective of a young patient (child) with beta thalassaemia. This may not be appropriate to inform health state utility values for adults with MDS and there were some concerns that the utility difference could have been overstated.
- Given the large difference in annual costs between the two devices used to administer desferrioxamine and the potential for bias, the SMC clinical experts were asked to comment on the appropriateness of the proportions of patients assumed to receive the Elastomeric balloon infuser vs. the automatic syringe infusion pump. Based on responses, there is some uncertainty surrounding the plausibility of the figures assumed in the base case.
- Taking account of the key sources of uncertainty, the company provided some combined scenario analyses which tested these issues simultaneously. If it was assumed that 50% of patients receive the Elastomeric balloon infuser and 50% receive the automatic syringe infusion pump, and also that 0% of deferasirox-treated patients transition into the transfusion independence health state, the ICER increased to £40,617 compared to desferrioxamine. The company also provided combined scenario analysis to show the effect of removing the transfusion-independence state and also assuming that the utility value associated with the desferrioxamine chelated health state was 0.79. The ICER rose to £50,857.

*Other data were also assessed but remain commercially confidential.**

## Impact beyond direct health benefits and on specialist services

At the PACE meeting it was highlighted that a well-tolerated oral chelation agent would improve quality of life and compliance with treatment. PACE participants noted the potential benefits would include:

- Physical benefit – Patients no longer have to experience the pain and discomfort associated with long term use of the needle and infusion pump which effectively turns the abdomen into a permanently sore and bruised area. Patients using the pump overnight find that they are unable to sleep properly because the noise of the pump disturbs them. The oral treatment option enables more patients to be fully mobile, to travel, and to be more active and/or carry out their daily routines as normal. This may

include the potential to return to work with the associated financial and psychological benefit.

- Psychological benefit – Use of the oral treatment option gives patients more control over managing their condition. Many patients on desferrioxamine refrain from social activities as they believe the pump is potentially embarrassing to wear in social situations. Not using the visible pump allows patients to avoid disclosing their illness if they so choose.
- Emotional benefit – The option of an oral treatment allows patients to live life to the full and be more positive about living with this condition.

Carers may be highly involved in the infusion process particularly where patients are unable to self administer, for example, if they have dexterity or sight issues. A dispersible, oral solution would remove the necessity for the patient's family or carer to administer the drug, ensuring more independence for the patient and relieving the carer of the task.

The economic analysis does not incorporate these wider effects.

## Costs to the NHS and Personal Social Services

The submitting company estimated there would be 95 patients eligible for treatment with deferasirox in all years to which confidential estimates of treatment uptake were applied.

The gross impact on the medicines budget was estimated to be £315k in year 1 and £472k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £191k in year 1, rising to £286k in year 5. After taking into account cost-offsets for with equipment associated with displaced medicines, the company estimated the overall net budget impact to be £21.6k and £37.5k in years 1 and 5 respectively.

*Other data were also assessed but remain commercially confidential.**

## Conclusion

The Committee considered the benefits of deferasirox in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as deferasirox is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted deferasirox for restricted use in NHS Scotland.

## Additional information: guidelines and protocols

The British Committee for Standards in Haematology published guidelines for the diagnosis and management of adult MDS, in 2014. Iron chelation therapy is not recommended for routine use in patients with MDS and transfusional iron overload. Iron chelation therapy should be considered in patients with a very good prognosis, ie, patients with World Health Organisation refractory anaemia, refractory anaemia with ringed sideroblasts and isolated del(5q). Triggers may include >20 units of red cells transfused and serum ferritin >1,000 micrograms/L in patients for whom continuing red cell transfusion is predicted. The guidelines note that ideally iron chelation therapy should be delivered within a clinical trial

setting. They note that desferrioxamine is the treatment of choice and that deferasirox is recommended for patients intolerant of desferrioxamine. Another agent, deferiprone, could be considered in patients with normal baseline neutrophil count.[3]

The National Comprehensive Cancer Network published clinical practice guideline, myelodysplastic syndromes in 2016. Iron chelation therapy should be considered in patients who have received more than 20 to 30 red blood cell transfusions particularly in patients with low or Int-1 IPSS. In patients with a serum ferritin level >2,500 micrograms/L, the aim is to reduce to <1,000 microgram/L. The guideline recommends daily subcutaneous desferrioxamine infusions or oral deferasirox. Use of either drug is not recommended in patients with a creatinine clearance <40mL/minute. [15]

## Additional information: comparators

Desferrioxamine.

## Cost of relevant comparators

| Drug | Dose regimen | Cost per year (£) |
|---|---|---|
| **deferasirox** | **10 to 40mg/kg orally once daily** | **9,173 to 33,634** |
| desferrioxamine | 20 to 60mg/kg by subcutaneous infusion or intramuscular injection up to seven days per week | 5,092 to 15,281 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26 August 2016. Costs are based on body weight of 70kg.

References

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This assessment is based on data submitted by the applicant company up to and including 14 October 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technologyappraisal:http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

***Advice context:***

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*