Deferasirox

Section: 10. Medicines affecting the blood > 10.3. Medicines for haemoglobinopathies

EMLc | ATC codes: V03AC03

Indication	Thalassaemias ICD11 code: 3A50.Z
INN	Deferasirox
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > dispersible tablet:** 100 mg ; 125 mg ; 250 mg ; 400 mg ; 500 mg **Oral > Solid > tablet:** 90 mg ; 180 mg ; 360 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	deferiprone (ATC codes: V03AC02)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Deferasirox
DrugBank	Deferasirox

Expert Committee recommendation

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. The Expert Committee noted that iron overload is a major concern for patients receiving regular blood transfusions; it is associated with multiorgan damage, particularly to the heart and liver, and leads to premature death if untreated. The Expert Committee considered this application together with a separate application requesting the addition of another iron chelating agent, deferiprone, for the treatment of transfusional iron overload in adults and children with thalassaemia syndromes, sickle-cell disease and other chronic anaemias. The Committee considered that the comparative efficacy and safety of deferiprone, deferoxamine and deferasirox are generally similar. The Committee considered that orally administered treatments may be preferred over intravenously administered deferoxamine. The Committee noted that deferasirox is available in innovator and generic brands as both film-coated tablets and dispersible tablets. Dispersible tablet formulations are considered important for administration to young children and other patients unable to swallow a solid dosage form. However, the two dosage forms are not bioequivalent on a milligram to milligram basis and so care must be taken to ensure appropriate dosing using the respective dosage forms. The Committee noted that the prices of iron chelating agents, and their availability, vary globally. Therefore, the Committee considered that having multiple iron chelating agents included on the Model Lists was important to enable countries to make appropriate national selection decisions taking into consideration relevant contextual factors. The Committee therefore recommended that the square box be removed from the current listing for deferoxamine, and that deferoxamine remain listed independently on the complementary list of the EML and EMLc. Because of the advantages offered by orally administered iron chelating agents, the Committee recommended deferasirox dispersible and film-coated tablets be transferred to the core list of the EML and EMLc, with a square box indicating oral deferiprone as a therapeutic

alternative. 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. The Expert Committee noted that iron overload is a major concern for patients receiving regular blood transfusions. It is associated with multiorgan damage, particularly to the heart and liver, and leads to premature death if untreated. Iron chelating agents deferoxamine (intravenous) and therapeutic alternative deferasirox (oral) have been included on the Model Lists for transfusional iron overload for more than 10 years. The Expert Committee considered this application together with the application requesting a change to the representative listed iron chelating agent from intravenous deferoxamine to oral deferasirox for the treatment of transfusional iron overload in adults and children with thalassaemia syndromes, sickle-cell disease and other chronic anaemias. The Committee considered that the available evidence supported the clinical efficacy of deferiprone in reducing serum ferritin and organ iron deposits. Evidence also indicated that it is generally well tolerated, with an acceptable safety profile. Furthermore, the Committee considered that the comparative efficacy and safety of deferiprone, deferoxamine and deferasirox were generally similar. The Committee noted that the prices of iron chelating agents, and their availability, vary globally. The Committee recognized the value in having multiple iron chelating agents included on the Model Lists to enable countries to make appropriate decisions on national selection, taking into consideration relevant contextual factors. The Expert Committee recommended that oral deferasirox be transferred to the core list of the EML and EMLc for use in the treatment of transfusional iron overload in patients with thalassaemia syndromes, sickle-cell disease and other chronic anaemias, with a square box listing specifying oral deferiprone as a therapeutic alternative. The Committee also recommended that intravenous deferoxamine remain listed on the complementary list of the EML and EMLc for these indications, and the square box associated with the current listing for deferoxamine be removed.

Background

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc.Deferoxamine has been included on the EML since 1979 as a treatment for acute iron poisoning and chronic iron overload. A review of iron chelating agents for acute and chronic iron poisoning, and treatment of sickle-cell disease was considered by the Expert Committee in 2011 (1). The Committee's findings and recommendations are summarized below. The Committee noted that a systematic review of observational and prospective studies suggested beneficial effects of deferoxamine on morbidity (notably cardiac disease and liver iron overload) and mortality, including subcutaneous use. In sickle-cell disease, evidence is more limited but supports the use of deferoxamine. Deferoxamine has adverse effects on growth and maturation, and auditory and ophthalmic function. The Committee considered that the main limitation of deferoxamine was however the need for prolonged parenteral administration, and a trial showed less compliance with parenteral deferoxamine than oral deferiprone. The Committee noted that the evidence supporting the use of deferiprone consisted of small trials – mostly observational including both adults and children and summarized in a Cochrane Review in 2007 (10 trials including 398 participants). The dose used in the trials was generally 75 mg/kg a day, and reported adverse effects included neutropenia and agranulocytosis, which require weekly monitoring of blood cell counts. Gastrointestinal symptoms are common and knee arthralgia is reversible. Neurological signs at doses of more than 100 mg/kg have been reported in children. The use of the combination of deferiprone and deferoxamine was found to be more effective than single agents with promising results of normalization of ferritinaemia. The review concluded that there was no consistent effect on reduction of iron overload among various treatments. Deferoxamine was more effective on iron excretion in three of four trials. The trials did not report on mortality or end-organ damage. The Committee concluded that the evidence supporting the effectiveness of deferiprone was insufficient. The evidence of effectiveness of deferasirox was more recent and of better quality than was the case for deferiprone. The Committee noted a large non-randomized uncontrolled prospective company-sponsored trial in 192 patients (64 aged younger than 16 years), which showed a statistically significant decrease in cardiac iron (assessed by magnetic resonance imaging) after 1 year of treatment. A Cochrane review of deferasirox in sickle-cell disease identified only one study and concluded that deferasirox appeared to be as effective as deferoxamine, but important outcomes were missing. No data were available to support the current use of deferasirox in

myelodysplastic syndromes. The Committee noted that deferasirox has renal adverse effects, which require regular monitoring of renal function. Dose-dependent increases in serum creatinine, which may occur in up to 36% of patients, may not always be reversible. Tubulopathy has also been reported in children with thalassaemia. The Committee considered the costs of deferoxamine, including laboratory monitoring costs, adverse effects and/or worsening of underlying disease as a result of non-compliance, hospitalization, parenteral injections, need for carers and missed school days. The cost of deferasirox treatment may be 2–3 times higher than that of deferoxamine, and the cost of deferiprone could be twice that of deferoxamine. The Committee noted that several reports suggest that deferasirox therapy is more cost-effective than traditional deferoxamine therapy, but considered that a truly unbiased cost comparison between deferiprone and deferasirox had not been published. The Committee noted that reports of cost analysis highlighted variations in acquisition costs and resources used. The acquisition cost of deferasirox is an important barrier to access, but adherence to infused deferoxamine is also problematic and administration costs also need to be considered. Although noting the advantages of the oral route, the Committee did not recommend the inclusion of deferasirox in the EML and EMLc at that stage, but recommended adding an asterisk to deferoxamine, noting the alternative oral form (deferasirox 500 mg dispersible oral solid dosage form) was available. 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. Deferiprone was previously considered by the Expert Committee in 2011 as part of a review of iron chelation therapy for acute iron poisoning in children (1). The outcome of this review was the listing of deferoxamine injection on the EML and EMLc as an antidote for acute iron poisoning and for treatment of sickle-cell disease. Oral deferasirox was noted as a therapeutic alternative for sickle-cell disease. Deferiprone was not recommended for listing. The Committee’s findings and recommendations are summarized below. The Committee noted that a systematic review of observational and prospective studies suggested beneficial effects of deferoxamine on morbidity (notably cardiac disease and liver iron overload) and mortality, including subcutaneous use. In sickle-cell disease, evidence is more limited but supports the use of deferoxamine. Deferoxamine has adverse effects on growth and maturation, and auditory and ophthalmic function. The Committee considered that the main limitation of deferoxamine was however the need for prolonged parenteral administration, and a trial showed less compliance with parenteral deferoxamine than oral deferiprone. The Committee noted that the evidence supporting the use of deferiprone consisted of small trials – mostly observational including both adults and children summarized in a Cochrane Review from 2007 (10 trials including 398 participants). The dose used in trials was generally 75 mg/kg a day, and reported adverse effects included neutropenia and agranulocytosis, which require weekly monitoring of blood cell counts. Gastrointestinal symptoms are common and knee arthralgia is reversible. Neurological signs at doses of more than 100 mg/kg have been reported in children. The use of the combination of deferiprone and deferoxamine was found to be more effective than single agents with promising results of normalization of ferritinaemia. The review concluded that there was no consistent effect on reduction of iron overload among various treatments. Deferoxamine was more effective on iron excretion in three of four trials. Trials did not report on mortality or end-organ damage. The Committee concluded that the evidence supporting the effectiveness of deferiprone was insufficient. The evidence of effectiveness of deferasirox was more recent and of better quality than was the case for deferiprone. The Committee noted a large non-randomized uncontrolled prospective company-sponsored trial in 192 patients (64 aged younger than 16 years), which showed a statistically significant decrease in cardiac iron (assessed by magnetic resonance imaging) after 1 year of treatment. A Cochrane review of deferasirox in sickle-cell disease identified only one study and concluded that deferasirox appeared to be as effective as deferoxamine, but important outcomes were missing. No data were available to support the current use of deferasirox in myelodysplastic syndromes. The Committee noted that deferasirox has adverse renal effects, which require regular monitoring of renal function. Dose-dependent increases in serum creatinine, which may occur in up to 36% of patients, may not always be reversible. Tubulopathy has also been reported in children with thalassaemia. The Committee considered the costs of deferoxamine, including laboratory monitoring cost, adverse effects and/or worsening of underlying disease as a result of non-compliance, hospitalization, parenteral injections, need for carers and missed school days. The cost of deferasirox treatment may be two to three times higher than that of deferoxamine, and the cost of deferiprone could be twice that of deferoxamine. The Committee noted that several reports suggest that deferasirox therapy

is more cost-effective than traditional deferoxamine therapy but considered that a truly unbiased cost comparison between deferiprone and deferasirox had not been published. The Committee noted that reports of cost analysis highlighted variations in acquisition costs and resources used. The acquisition cost of deferasirox is an important barrier to access, but adherence to infused deferoxamine is also problematic and administration costs also need to be considered. Although noting the advantages of the oral route, the Committee did not recommend the inclusion of deferasirox in the EML and EMLc at that stage, but recommended adding an asterisk to deferoxamine, noting the alternative oral form (deferasirox 500 mg dispersible oral solid dosage form) was available.

Public health relevance

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. Iron overload is generally the result of disorders such as thalassaemia or sickle-cell disease, which are associated with repeated blood transfusions. It is also associated with hereditary haemochromatosis and other conditions such as porphyria that affect iron absorption or regulation. Thalassaemia is an inherited blood disorder characterized by reduced haemoglobin and depleted red blood cells. Thalassaemia results in the inability to form functional haemoglobin, leading to life-threatening anaemia. Patients require life-long blood transfusions, resulting in iron overload (2). The global prevalence of thalassaemia in 2019 was 13.7/100 000 (all ages), with the highest prevalence in South-east Asia, East Asia and Oceania, and the lowest prevalence in Latin America and the Caribbean (3). Sickle-cell disease is a hereditary condition that affects haemoglobin, generating an altered form of the protein known as haemoglobin S (HbS). Polymerization of HbS may occur, leading to sickle-like deformation of red blood cells, vascular obstruction, pain and organ damage. Blood transfusions are an important supportive therapy for treatment and prevention of sickle cell disease complications. Repeated transfusions can lead to iron overload (4). The global prevalence of sickle-cell disorders in 2019 was 73.57/100 000 (all ages), with the highest prevalence in sub-Saharan Africa (3), where an estimated 240 000 babies with HbS are born each year (5). Hereditary haemochromatosis is an inherited disorder of iron metabolism which can lead to increased systemic iron concentrations as a consequence of excessive intestinal absorption of dietary iron. Prevalence estimates using genetic screening range from 0.00006% (6) to 2.3% (7). Porphyrias are metabolic disorders characterized by a genetically determined enzymatic defect in the haem biosynthesis pathway. They are associated with serum ferritin accumulation and iron overload. The global prevalence of porphyria has been reported to be 53 per million people (8). 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. Sickle-cell disease is a multisystem disorder that affects almost every organ in the body. It is characterized by the presence of sickle haemoglobin which causes sickle-shaped erythrocytes. It is a life-threatening disease that leads to haemolytic anaemia and blockages in small blood vessels, which may potentially lead to ischaemia, infarction and organ damage (2). Sickle-cell disease is one of the most common haemoglobinopathies worldwide and is recognized by WHO as a global public health problem (3). Worldwide in 2019, 605 00 people were born with sickle-cell disorders, an estimated 5.7 million people were living with sickle-cell disorders and 42 000 people died as a result of sickle-cell disorders (all ages) (4). The prevalence of sickle-cell disorders varies by region and is highest in Africa, Mediterranean countries and the Middle East (5,6). More than half of all individuals living with sickle cell disorders live in sub-Saharan Africa or India (5). The condition β-thalassaemia is an inherited haemoglobinopathy in which the reduced or absent production of functional haemoglobin results in severe and life-threatening anaemia. The annual incidence of symptomatic individuals with β-thalassaemia is estimated to be 1 in 100 000. The incidence of β-thalassaemia varies by region. About 60 000 people are born each year with symptomatic β-thalassaemia. The prevalence is highest in the Mediterranean region, the Middle East, central Asia, India, southern China, and east and south-east Asia (7). Blood transfusions are one of the cornerstones in the management of sickle-cell disease and β-thalassaemia. A main cause of morbidity in patients with these conditions is iron overload due to chronic blood transfusions (8–10). Untreated or inadequately treated iron overload can lead to complications such as liver fibrosis and cirrhosis, hepatocellular carcinoma, cardiomyopathy and endocrine disorders (11–13).

Benefits

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. The application presented the findings of multiple meta-analyses of randomized studies comparing the efficacy and safety of deferoxamine and deferasirox. A Cochrane systematic review of nine randomized controlled trials (1251 participants) comparing deferasirox and deferoxamine for management of iron overload in people with thalassaemia reported that similar efficacy can be achieved depending on the ratio of doses of deferasirox and deferoxamine being compared (9). Deferasirox was not superior to deferoxamine at the usually recommended dose ratio of 1 mg to 2 mg. Pooled effects across different dosing ratios reported heterogeneous findings that could potentially be explained by the use of different dosing ratios. Patient satisfaction with treatment favoured deferasirox. The authors concluded that deferasirox could be offered as the first-line option to individuals who show strong preference for deferasirox, and that it may be a reasonable treatment option for patients intolerant of or poorly adherent to deferoxamine, following detailed discussion of potential benefits and risks. A Cochrane systematic review of two randomized controlled trials (415 participants) compared the efficacy and safety of deferasirox and deferoxamine for management of transfusional iron overload in patients with sickle-cell disease (10). Serum ferritin reduction was similar in both groups (mean difference (MD) 375.00 micrograms/L in favour of deferoxamine, 95% confidence interval (CI) –106.08 to 856.08). No difference was observed between treatments for liver ion concentration for the overall group of patients (MD –0.20 mg Fe/g dry weight, 95% CI –3.15 to 2.75 Fe/g dry weight). Patient satisfaction and convenience of treatment were significantly better with deferasirox. A Cochrane systematic review of 16 randomized controlled trials (1525 participants) assessed interventions for improving adherence to iron chelation therapy in people with sickle-cell disease or thalassaemia (11). One included trial compared deferasirox and deferoxamine monotherapy, in which adherence rates were high for both treatment groups, but from which it was not possible to determine a difference in adherence between treatment groups (MD –1.40, 95% CI –3.66 to 0.86). A multiple treatment comparison network meta-analysis of 32 clinical trials compared the efficacy and safety of different iron chelators (monotherapy and combination) in patients with thalassaemia or sickle-cell disease (12). Relative estimates suggested that combination therapy with deferasirox and deferoxamine was associated with better serum ferritin and lower liver iron concentrations compared with deferoxamine monotherapy; however, the strength of evidence was very low for most comparisons. A meta-analysis of six studies comparing deferasirox with deferoxamine and placebo evaluated the effectiveness and safety of deferasirox in patients with thalassaemia (13). For the outcome of reduction of liver iron concentration, deferasirox was more effective than deferoxamine when given at a dose of 30 mg/kg a day (MD –2.5, 95% CI –4.55 to –0.45). At all other doses (5, 10, 20 and 40 mg/kg a day), deferoxamine was more effective than deferasirox. Pooled analysis across all doses showed no significant difference between treatments. Similar findings were observed for the outcome of serum ferritin reduction. The application also presented summaries of individual randomized controlled trials included in the above-mentioned systematic reviews and meta-analyses and other clinical studies (4,14–25). The applicants conclude that the body of evidence suggests that deferasirox is as effective as deferoxamine in clinical practice for treatment of chronic iron overload conditions and offers relevant advantages of oral compared with parenteral administration. 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. Sickle-cell disease The application presented the findings of a systematic literature review and network meta-analysis which indirectly compared deferiprone, deferasirox and deferoxamine in patients with sickle-cell disease. Efficacy endpoints were change from baseline to 12 months in liver iron concentration and serum ferritin. Two randomized, open-label trials (423 participants) were included (14,15). Liver iron concentration In the intention-to-treat population, the mean difference (MD) from baseline to 12 months relative to deferiprone was –0.40 (95% credible Interval (CrI) –1.70 to 0.89) for deferoxamine and –0.68 (95% CrI –3.63 to 2.25) for deferasirox. The MD relative to deferiprone using the sickle-cell disease subpopulation was –0.58 (95% CrI –1.83 to 0.66) for deferoxamine and –0.84 (95% CrI –3.74 to 2.19) for deferasirox. The MD relative to deferiprone using the subpopulation with serum creatinine lower than the upper limit of normal was –0.43 (95% CrI –1.70 to 0.85) for deferoxamine and –0.72 (95% CrI –3.86 to 2.25) for deferasirox. No statistically significant differences between deferiprone and deferoxamine or deferasirox were found, nor between

deferoxamine and deferasirox. Serum ferritin In the intention-to-treat population, the MD from baseline to 12 months relative to deferiprone was –364.39 (95% CrI –961.37 to 237.22) for deferoxamine and 11.15 (95% CrI –688.24 to 712.52) for deferasirox. Deferoxamine was numerically preferable to deferasirox (MD –376.15, 95% CrI –739.09 to –5.29). For the sickle-cell disease subpopulation, the MD relative to deferiprone was –556.18 (95% CrI –1217.68 to 117.79) for deferoxamine and –182.56 (95% CrI –942.53 to 588.51) for deferasirox. Deferoxamine was numerically preferable to deferasirox (MD –374.70, 95% CrI –738.39 to –7.08). For the subpopulation with serum creatinine lower than the upper limit of normal, the MD relative to deferiprone was –387.68 (95% CrI –994.05 to 211.54) for deferoxamine and –12.77 (95% CrI –724.22 to 692.78) for deferasirox. Deferoxamine was numerically preferable to deferasirox (MD –373.59, 95% CrI –740.39 to –6.34). β-thalassaemia The application presented the findings of a systematic literature review and network meta-analysis that indirectly compared deferiprone, deferasirox and deferoxamine in patients with β-thalassaemia. Efficacy endpoints were change from baseline to 12 months in liver iron concentration, serum ferritin, cardiac MRI T2* and left ventricular ejection fraction (LVEF). Six randomized trials (1129 participants) were included (16–21). Liver iron concentration Four randomized controlled trials reported on liver iron concentration (16,17,20,21). Pooled analysis of two randomized controlled trials comparing deferiprone and deferoxamine monotherapy (16,17) showed no significant difference between treatments on liver iron concentration (weighted MD –0.16 mg/g dry weight (95% confidence interval (CI) –1.39 to 1.06 mg/g). An indirect comparison of deferiprone and deferasirox via deferoxamine showed no statistically significant difference between treatment arms. One randomized controlled trial comparing deferiprone–deferoxamine sequential therapy with deferoxamine monotherapy reported no statistically significant difference between treatment arms, although the effect was numerically larger in the deferoxamine monotherapy arm. An indirect comparison of deferiprone–deferoxamine sequential therapy with deferiprone monotherapy showed no statistically significant difference. Serum ferritin Five randomized controlled trials reported on serum ferritin (16,17,19–21). Pooled analysis of two randomized controlled trials comparing deferiprone and deferoxamine monotherapy (16,17) showed no significant difference between treatments on serum ferritin levels (weighted MD 92.56, 95% CI –154.49 to 339.61). An indirect comparison of deferiprone and deferasirox via deferoxamine showed deferiprone to be significantly more effective, while an indirect comparison via deferiprone-deferoxamine sequential therapy did not show a significant difference. Meta-analyses of the randomized controlled trial comparing deferasirox and deferoxamine (21) showed high heterogeneity between subgroups with different baseline liver iron concentration levels, in which smaller differences in effect size were observed for patients with higher baseline liver iron concentration. To test the effect of this heterogeneity on the indirect comparison of deferiprone and deferasirox, a sensitivity analysis including only patients with baseline liver iron concentration ≥ 7 mg/g dry weight was conducted, which suggested deferiprone and deferasirox were equally efficacious in their effect on serum ferritin. One randomized controlled trial comparing sequential deferiprone–deferoxamine and deferoxamine monotherapy showed no significant difference in effect on serum ferritin. Another randomized controlled trial comparing sequential deferiprone–deferoxamine and deferiprone monotherapy showed a greater improvement in serum ferritin with sequential therapy compared with deferiprone monotherapy (weighted MD –285.00, 95% CI –495.46 to –74.54). Cardiac T2* Two randomized controlled trials reported log-transformed cardiac MRI T2* (16,18). One trial comparing deferiprone and deferoxamine showed a significant improvement in cardiac iron in patients treated with deferiprone compared with deferoxamine (ratio of geometric means 1.12, 95% CI 1.07 to 1.17) (16). One trial comparing deferiprone–deferoxamine combination therapy versus deferoxamine monotherapy showed a significant improvement in cardiac iron for the combination therapy arm (ratio of geometric means 1.1, 95% CI 1.2 to 1.19) (18). Indirect comparison of deferiprone versus deferiprone–deferoxamine combination therapy (via deferoxamine monotherapy) showed no significant difference in effect between treatments (ratio of geometric means 0.98, 95% CI 0.89 to 1.08). Left ventricular ejection fraction Two randomized controlled trials reported improvements in left ventricular ejection fraction in patients treated with deferiprone compared with deferoxamine (16,17). A random-effects meta-analysis showed deferiprone was associated with a 2.1% greater absolute improvement in left ventricular ejection fraction compared with deferoxamine (weighted MD 0.02, 95% CI 0.00 to 0.04). One randomized controlled trials comparing deferiprone–deferoxamine combination therapy with deferoxamine alone (18), and indirectly comparing combination therapy with deferiprone monotherapy (via deferoxamine monotherapy), did not show statistically significant differences

between treatments. Combination therapy Evidence supports the use of combination therapy with iron chelating agents to increase the effectiveness of treatment in patients who do not adequately respond to monotherapy, or when prevention or treatment of life-threatening consequences of iron overload justifies rapid intensive correction (18–20,22–24). Combination therapy is also recommended for certain patients in the guidelines of the Thalassaemia International Federation (13) and the British Society for Haematology (25).

Harms

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. Deferoxamine and deferasirox have been available on the market for many years, with annual patient exposures of about 7000–8000 patient treatment-years and 50 000–55 000 patient treatment-years, respectively. Their safety profiles are well known. A summary of adverse events reported in clinical studies and in postmarketing, as reported in approved United Kingdom prescribing information (26,27) was presented in the application. For deferoxamine, common and very common adverse reactions include headache, nausea, urticaria, arthralgia, myalgia, growth retardation, bone disorders, injection site pain, swelling, infiltration, erythema, pruritus, eschar and pyrexia. For deferasirox, common and very common adverse reactions include headache, gastrointestinal effects, increased transaminases, rash, pruritus, increased blood creatinine and proteinuria. Deferasirox may cause acute kidney injury (including acute renal failure requiring dialysis and renal tubular toxicity including Fanconi syndrome), hepatic toxicity and gastrointestinal haemorrhage. Therapy with deferasirox therefore requires close patient monitoring, including laboratory tests of renal and hepatic function (27,28). A Cochrane systematic review of nine randomized controlled trials (1251 participants) comparing deferasirox and deferoxamine for management of iron overload in people with thalassaemia reported no statistically significant difference in mortality, serious adverse events, or any adverse events between treatment groups (9). Increases in creatinine occurred significantly more often with deferasirox than deferoxamine. Satisfaction with, convenience of and willingness to continue treatment was significantly higher in patients receiving deferasirox who had previously received deferoxamine, and time lost from normal activities due to treatment was significantly less with deferasirox. Adherence, defined as the percentage of the planned dose taken by participants, was evaluated in one study with no significant difference observed between treatment groups (23). Data from randomized trials on rare toxicities and long-term safety are still limited. A Cochrane systematic review of two randomized controlled trials (415 participants) comparing the efficacy and safety of deferasirox and deferoxamine for management of transfusional iron overload in patients with sickle-cell disease (10) reported that the occurrence of serious adverse events did not differ between treatment groups. Nausea, diarrhoea and rash occurred significantly more often in patients treated with deferasirox, any adverse events were reported more often in patients treated with deferoxamine. A review of the safety of iron chelation therapies in young patients (< 25 years) with haemoglobinopathies (34 studies, 2040 participants) (29) found that iron chelation therapy was generally safe in young patients and in line with the safety data reported in the summaries of product characteristics. Discontinuation rates due to severe or serious adverse events were generally low for all regimens. A meta-analysis of six studies evaluating the effectiveness and safety of deferasirox in patients with thalassaemia (13) found a significantly higher risk of increased serum creatinine (risk ratio (RR) 2.69, 95% CI 1.98 to 3.67) and alanine transaminase (RR 5.67, 95% CI 1.01 to 31.79) with deferasirox compared with deferoxamine. Gastrointestinal events, rash and serious adverse events were more common with deferasirox than deferoxamine, but differences were not statistically significant. No statistically significant difference was found between treatments for mortality. 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. Sickle-cell disease The most common adverse reactions reported during clinical trials occurring in ≥ 5% of patients treated with deferiprone include pyrexia (28%), abdominal pain (26%), bone pain (25%), headache (20%), vomiting (19%) and extremity pain (18%). Clinically relevant adverse reactions occurring in < 5% of patients treated with deferiprone include neutropenia and agranulocytosis (26). In patients treated with deferiprone in the FIRST trial, those with sickle-cell disease and other anaemias who received deferiprone were more likely to experience a treatment-related increase in alanine aminotransferase compared with patients who received deferoxamine (9.2% versus

0%) (14). In an Italian randomized controlled trial comparing deferiprone with deferoxamine in sickle-cell disease, 10% of patients receiving deferiprone experienced liver damage or increased alanine aminotransferase more than twice the normal value, compared with no patients treated with deferoxamine (27). Greater increases in serum creatinine have been reported with deferasirox compared with deferoxamine (6.3 micromol/L versus 3.06 micromol/L, respectively) (15). Neutropenia and agranulocytosis were more commonly reported in studies evaluating deferiprone, with the percentage of patients affected ranging from 5.9% to 9.0% for neutropenia and 0% to 1.5% for agranulocytosis. β-thalassaemia The most common adverse reactions reported during clinical trials occurring in ≥ 5% of patients treated with deferiprone include nausea (12.6%), abdominal pain (10.0%), vomiting (9.8%), arthralgia (9.8%), increased alanine aminotransferase (7.5%) and neutropenia (6.2%) (26,28). A lack of consistent data-reporting prevented robust statistical analysis of safety data in randomized controlled trials on β-thalassaemia. Combination therapy Clinical experience with combination use of deferiprone and deferoxamine suggests no significant toxicity issues with the combination (29). Adverse events associated with combination therapy with deferiprone and deferasirox were reported to be consistent with those reported for component monotherapy. The most common adverse events included gastrointestinal symptoms, elevation in alanine aminotransferase and/or aspartate aminotransferase, arthralgia/joint symptoms, increased serum creatinine, proteinuria and red-coloured urine. The number of patients experiencing neutropenia or thrombocytopenia was low (30). Paediatric use A study with 100 children aged 1–10 years with transfusion-dependent anaemia treated with deferiprone oral solution did not identify any new safety concerns compared with other studies of deferiprone tablets in older children and adults (31). In a randomized controlled trial comparing deferiprone and deferasirox in paediatric patients aged 1 month to 18 years with transfusion-dependent haemoglobinopathies, deferiprone had an acceptable safety profile. No significant differences were seen between treatment arms in serious and drug-related adverse events. Adverse events were similar to those seen in the adult population. No safety concerns in very young children were identified (22).

Cost / cost effectiveness

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. National prices for deferoxamine and deferasirox dispersible tablets in least developed, lower middle-income and upper middle-income countries were reported in the application as summarized in Table 18 (refer TRS 1049). National prices for deferoxamine, deferasirox dispersible tablets and deferasirox film-coated tablets in high-income countries were reported in the application as summarized in Table 19 (refer TRS 1049). A 2017 cost–utility analysis of iron chelators as monotherapy for chronic iron overload in patients with β-thalassaemia major from an Italian health care system perspective found deferiprone to be dominant and the most cost-effective treatment, and deferasirox to produce a higher quality-adjusted life year gained than deferoxamine but with a greater total cost (42). A 2020 cost–utility analysis of film-coated deferasirox versus deferoxamine in patients with β-thalassaemia from a payer perspective in the Islamic Republic of Iran explored two scenarios based on age at starting treatment (2 years or 18 years), estimating lifetime costs and utilities (43). Deferasirox film-coated tablets produced an incremental cost–effectiveness ratio of US$ 1470.60 and US$ 2544.70, respectively for starting treatment at 2 years and 18 years, compared with branded deferoxamine. The incremental cost–effectiveness ratios for deferasirox compared with generic deferoxamine were US$ 2837.09 and US$ 6924.13, respectively, for starting treatment at 2 years and 18 years. A cost–utility analysis from the Chinese health care perspective also evaluated the cost–effectiveness of four chelation regimens for β-thalassaemia major (44). Deferiprone was also found to be the most cost-effective chelation regimen, followed by deferoxamine, deferasirox and combination therapy. Deferoxamine administration costs were estimated to range between US$ 2000/year and US$ 3500/year. Monitoring costs were estimated to be US$ 20–200/year for deferoxamine and US$ 100–400/year for deferasirox (42–44). 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. A systematic review of 19 cost–utility studies evaluated the cost–effectiveness of four chelation regimens for β-thalassaemia major therapy – deferoxamine, deferiprone or deferasirox monotherapy, and deferoxamine + deferiprone combination therapy (42). Deferiprone was found to be cost-effective compared with deferasirox in three studies,

compared with deferoxamine in three studies, and compared with combination therapy in one study. The authors concluded that for iron chelator monotherapy, deferiprone was the most cost-effective option, followed by deferoxamine and deferasirox. However, the authors noted substantial differences in costs between countries and regions and that the local economic context played a substantial role in the results of the pharmacoeconomic evaluation. National prices for iron chelators are summarized in Table 20 (refer TRS 1049). A cost–utility analysis from the Chinese health care perspective also evaluated the cost–effectiveness of four chelation regimens for β-thalassaemia major (43). This study also found deferiprone to be the most cost-effective chelation regimen, followed by deferoxamine, deferasirox and combination therapy.

WHO guidelines

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. WHO guidelines for treatment of transfusional iron overload in patient with sickle-cell disorders, β-thalassaemia or other anaemias are not currently available. The use of iron chelating agents for the treatment of transfusional iron overload is recommended in many national and international guidelines (30–41). 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. WHO guidelines for the treatment of transfusional iron overload in patient with sickle-cell disorders, β-thalassaemia or other anaemias are not currently available. The use of iron chelating agents for the treatment of transfusional iron overload is recommended in multiple national and international guidelines (13,25,32–41).

Availability

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. The application reported that branded deferoxamine is marketed in 65 countries in the world. Generic brands are also available. Deferoxamine has been deregistered in 16 countries in the past 15 years. Branded deferasirox (as dispersible or film-coated tablets) is marketed in 95 countries in the world. Generic brands are also available. Since the introduction to the market of deferasirox film-coated tablets, deferasirox dispersible tablets have been discontinued in some countries. 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. Immediate-release deferiprone has marketing authorization in more than 30 countries. Generic brands are available in some settings. Currently, the modified-release deferiprone formulation is only approved and marketed in the United States, but is reported to be undergoing regulatory consideration in other countries.

Other considerations

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc. A separate application to the 2023 Expert Committee meeting requested listing of oral deferiprone as a therapeutic alternative to deferoxamine for the treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. 2. Application for the addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias. A separate application to the 2023 Expert Committee meeting requested a change to current listing for intravenous deferoxamine for treatment of haemoglobinopathies, to make oral deferasirox the representative iron chelating agent under the square box listing.

1. Application to change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc.

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