Deferoxamine

Essential medicine status ✓

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

EMLc | ATC codes: V03AC01

Indication	Other specified sickle cell disorders or other haemoglobinopathies — ICD11 code: 3A51.Y
INN	Deferoxamine
Medicine type	Chemical agent
List type	Complementary (EML) (EMLc)
Formulations	Parenteral > General injections > unspecified: 500 mg in vial powder for injection (mesilate)
EML status history	First added in 2011 (TRS 965) Changed in 2021 (TRS 1035) Changed in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Deferoxamine
DrugBank	Deferoxamine

Expert Committee recommendation

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.

Background

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.

Public health relevance

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).

Benefits

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.

Harms

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.

Cost / cost effectiveness

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).

WHO guidelines

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).

Availability

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.

Other considerations

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.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2011 (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2012 (WHO Technical Report Series, No. 965; https://apps.who.int/iris/handle/10665/44771, accessed 6 October 2023).
2. Kuo KHM, Mrkobrada M. A systematic review and meta-analysis of deferiprone monotherapy and in combination with deferoxamine for reduction of iron overload in chronically transfused patients with β-thalassemia. Hemoglobin. 2014;38(6):409–21.
3. Global Burden of Disease database [internet]. Seattle, WA: Institute for Health Metrics and Evaluation; 2019 (https://vizhub.healthdata.org/gbd-results/, accessed 6 October 2023).
4. Vichinsky E, Torres M, Minniti CP, Barrette S, Habr D, Zhang Y, et al. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: two-year results including pharmacokinetics and concomitant hydroxyurea. Am J Hematol. 2013;88(12):1068–73.
5. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013;381(9861):142–51.
6. Wallace DF, Subramaniam VN. The global prevalence of HFE and non-HFE hemochromatosis estimated from analysis of next-generation sequencing data. Genet Med. 2016;18(6):618–26.
7. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/331505, accessed 6 October 2023).
8. Prevalence and incidence of rare diseases: bibliographic data. Paris: Orphanet; 2022 (https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf, accessed 6 October 2023).
9. Bollig C, Schell LK, Rücker G, Allert R, Motschall E, Niemeyer CM, et al. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database Syst Rev. 2017;8(8):CD007476.
10. Meerpohl JJ, Antes G, Rücker G, Fleeman N, Niemeyer C, Bassler D. Deferasirox for managing transfusional iron overload in people with sickle cell disease. Cochrane Database Syst Rev. 2010(8):CD007477.
11. Fortin PM, Fisher SA, Madgwick KV, Trivella M, Hopewell S, Doree C, et al. Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia. Cochrane Database Syst Rev. 2018;5(5):Cd012349.
12. Sridharan K, Sivaramakrishnan G. Efficacy and safety of iron chelators in thalassemia and sickle cell disease: a multiple treatment comparison network meta-analysis and trial sequential analysis. Expert Rev Clin Pharmacol. 2018;11(6):641–50.
13. Dou H, Qin Y, Chen G, Zhao Y. Effectiveness and safety of deferasirox in thalassemia with iron overload: a meta-analysis. Acta Haematol. 2019;141(1):32–42.
14. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. 2006;107 (9):3455–62.
15. Al-Kuraishy H, Al-Gareeb A. Comparison of deferasirox and deferoxamine effects on iron overload and immunological changes in patients with blood transfusion-dependent β-thalassemia. Asian J Transfus Sci. 2017;11(1):13–7.
16. Ansari S, Azarkeivan A, Miri-Aliabad G, Yousefian S, Rostami T. Comparison of iron chelation effects of deferoxamine, deferasirox, and combination of deferoxamine and deferiprone on liver and cardiac T2* MRI in thalassemia maior. Caspian J Intern Med. 2017;8(3):159–64.
17. Chirico V, Lacquaniti A, Salpietro V, Luca N, Ferraù V, Piraino B, et al. Thyroid dysfunction in thalassaemic patients: ferritin as a prognostic marker and combined iron chelators as an ideal therapy. Eur J Endocrinol. 2013;169(6):785–93.
18. Goulas V, Kouraklis-Symeonidis A, Manousou K, Lazaris V, Pairas G, Katsaouni P, et al. A multicenter cross-sectional study of the quality of life and iron chelation treatment satisfaction of patients with transfusion-dependent β-thalassemia, in routine care settings in Western Greece. Qual Life Res. 2021;30(2):467–77.
19. Habibian N. Comparison of therapeutic effect of osveral & desferal in patients with thalassemia (Bahonar hospital in Karaj 2012–2013). Iran J Pediatr. 2014;24(2):27.
20. Hassan MAM, Tolba OA. Iron chelation monotherapy in transfusion-dependent beta-thalassemia major patients: a comparative study of deferasirox and deferoxamine. Electron Physician. 2016;8(5):2425–31.
21. Molavi MA, Doozandeh H, Nazemi AM, Evazi R, Mansoori F. Comparison of therapeutic response and complications of oral osveral and injection desfereal chelating agent in patient with thalassemia major. Asian J Med Pharm Res. 2013;3(3):93–7.
22. Peng P, Long L, Huang Z, Zhang L, Li X, Feng X, et al. Comparison of deferasirox and deferoxamine treatment in iron-overloaded patients: Liver iron concentration determined by quantitative MRI-R2*. Chinese J Radiol. 2013;47(1):55–9.
23. Pennell DJ, Porter JB, Piga A, Lai Y, El-Beshlawy A, Belhoul KM, et al. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in β-thalassemia major (CORDELIA). Blood. 2014;123(10):1447–54.
24. Piga A, Galanello R, Forni GL, Cappellini MD, Origa R, Zappu A, et al. Randomized phase II trial of deferasirox (Exjade, ICL670), a once-daily, orally-administered iron chelator, in comparison to deferoxamine in thalassemia patients with transfusional iron overload. Haematologica. 2006;91(7):873–80.
25. Vichinsky E, Onyekwere O, Porter J, Swerdlow P, Eckman J, Lane P, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol. 2007;136(3):501–8.
26. Desferal. Summary of product characteristics. London: Medicines and Healthcare products Regulatory Agency; 2020 (https://mhraproducts4853.blob.core.windows.net/docs/7148743ba832bb28de12707e9d43a949535e2132, accessed 6 October 2023).
27. Exjade Summary of product characteristics. London: Medicines and Healthcare products Regulatory Agency; 2022 (https://mhraproducts4853.blob.core.windows.net/docs/ab988c473907557582dfae31c4a6ae03cc0617f8, accessed 6 October 2023).
28. Prescribing Information. EXJADE (deferasirox) tablets for oral suspension. U.S. Food and Drug Administration; revised July 2020 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021882s033lbl.pdf, accessed 6 October 2023).
29. Botzenhardt S, Li N, Chan EW, Sing CW, Wong IC, Neubert A. Safety profiles of iron chelators in young patients with haemoglobinopathies. Eur J Haematol. 2017;98(3):198–217.
30. Cappenelli MD, Farmakis D, Porter J, Taher A, editors. Guidelines for the management of transfusion dependent thalassemia (TDT). Fourth edition (version 2.0). Strovolos: Thalassaemia International Federation; 2021.
31. Ho PJ, Tay L, Lindeman R, Catley L, Bowden DK. Australian guidelines for the assessment of iron overload and iron chelation in transfusion-dependent thalassaemia major, sickle cell disease and other congenital anaemias. Intern Med J. 2011;41(7):516–24.
32. Veríssimo MP, Loggetto SR, Fabron Junior A, Baldanzi GR, Hamerschlak N, Fernandes JL, et al. Brazilian Thalassemia Association protocol for iron chelation therapy in patients under regular transfusion. Rev Bras Hematol Hemoter. 2013;35(6):428–34.
33. Sickle cell disease consensus statement [internet]. Canadian Haemoglobinopathy Association; 2018 (https://www.canhaem.org/scd-consensus-statement/, accessed 6 October 2023).
34. Protocole National de Diagnostic et de Soins (PNDS). Syndromes thalassémiques majeurs et intermédiaires. Texte du PNDS. Filière de santé maladies rares [National Diagnostic and Care Protocol (PNDS). Major and intermediate thalassemia syndromes. Text of the PNDS. Rare diseases health sector]. MCGRE; 2021 (https://www.has-sante.fr/upload/docs/application/pdf/2021-07/pnds_syndromes_thalassemiques_majeurs_et_intermediaires.pdf, accessed 6 October 2023).
35. Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, et al. Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. Haematologica. 2008;93(5):741–52.
36. Casale M, Casciana ML, Ciliberti A, Colombatti R, Vecchio CD, Fasoli S, et al. Linee-Guida Per La Gestione Della Malattia Drepanocitica in Eta ‘ Pediatrica in Italia [Guidelines for the management of pediatric sickle cell disease in Italy] [internet]. Associazione Italiana Ematologia Oncologia Pediatrica; 2018 (https://www.aieop.org/web/operatori-sanitari/linee-guida-consensum/, accessed 6 October 2023).
37. Evidence-based management of sickle cell disease. Expert panel report, 2014. National Heart, Lung, and Blood Institute. Washington, DC: United States Department of Health and Human Services (https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf, accessed 6 October 2023).

38. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327–55.
39. Clinical Commissioning Policy: treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias (all ages). London: NHS England; 2022 (https://www.england.nhs.uk/publication/clinical-commissioning-policy-treatment-of-iron-overload-for-transfused-and-non-transfused-patients/, accessed 6 October 2023).
40. Shah FT, Porter JB, Sadasivam N, Kaya B, Moon JC, Velangi M, et al. Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias. Br J Haematol. 2022;196(2):336–50.
41. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. Br J Haematol. 2017;176(2):192–209.
42. Pepe A, Rossi G, Bentley A, Putti MC, Frizziero L, D'Ascola DG, et al. Cost-utility analysis of three iron chelators used in monotherapy for the treatment of chronic iron overload in β-thalassaemia major patients: an Italian perspective. Clin Drug Investig. 2017;37(5):453–64.
43. Saiyarsarai P, Khorasani E, Photogeraphy H, Ghaffari Darab M, Seyedifar M. Cost-utility of new film-coated tablet formulation of deferasirox vs deferoxamine among major beta-thalassemia patients in Iran. Medicine. 2020;99(28):e20949–e.
44. Li J, Wang P, Li X, Wang Q, Zhang J, Lin Y. Cost-utility analysis of four chelation regimens for β-thalassemia major: a Chinese perspective. Mediterr J Hematol Infect Dis. 2020;12(1):e2020029.