NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Technology Appraisal

Desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia.

Background

Iron overload occurs when excess iron collects in the body. As there are no natural means of removing excess iron, iron gradually accumulates. Excess unbound (free) iron deposits in the tissues of the liver, endocrine organs and heart. The complications include liver cirrhosis, endocrine complications such as diabetes, impaired growth in children, sterility, and cardiomyopathy (heart failure). Chronic iron overload therefore increases mortality risk. Iron overload can be caused by excessive absorption of iron from diet or more commonly through frequent blood transfusions.

Blood transfusions represent lifesaving therapy for patients with chronic anaemia, such as those suffering from thalassaemia. Thalassaemia is the name given to a group of inherited blood disorders that cause the body to make fewer healthy red blood cells and less haemoglobin. There are two basic groups of thalassaemia disorders: alpha-thalassaemia and beta-thalassaemia. These conditions cause varying degrees of anaemia, which can range from insignificant to life threatening. The most severe forms are known as alpha- or beta-thalassaemia major and the least severe forms as alpha- or beta-thalassaemia minor. Thalassaemia minor does not usually require any specific treatment but thalassaemia major involves frequent blood transfusions (possibly eight or more each year). People with thalassaemia are at risk of collecting excess iron in their bodies, both from the disease itself and from the multiple blood transfusions that they receive. The prevalence of thalassaemia varies across different ethnic communities. It is estimated that around 3-10% people of Indian origin, 4.5% of Pakistani origin, 8% of Bangladeshi origin, 17% of Cypriotic origin, 0.5-1% of Afro-Caribbean origin, and 0.1% of White people carry thalassaemia.

Total body iron stores are usually within the range of 3 – 4 grams. Each unit of transfused blood contains 200-250 mg of iron, all of which cannot be excreted. The risk of iron overload increases once patients have received approximately 20 transfusions. A patient with a high transfusion requirement, defined as 3-4 units of blood per month (such as given in beta-thalassaemia

major), will need iron chelation therapy after 6 months. The timing for children will depend on the transfusion frequency and amount of blood being transfused. Data provided by the UK thalassaemia register, which ceased recording in 2003, suggested there were 624 beta thalassaemia major patients at risk of iron overload at that time, plus *"a small proportion"* of the 162 patients registered with other beta thalassaemias.

In the UK the current treatment options for patients with thalassaemia major presenting with transfusion-related iron overload are three iron chelating agents as outlined below.

The technologies

Desferrioxamine

Desferrioxamine mesilate (Desferal, Novartis; Desferrioxamine mesilate, Hospira) has a UK marketing authorisation for the treatment of chronic iron overload, including acute iron poisoning; primary and secondary haemochromatosis including thalassaemia and transfusional haemosiderosis; in patients in whom concomitant disorders (for example, severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy; and for the diagnosis of iron storage disease and sideroblastic anaemia, auto-immune haemolytic anaemia and other chronic anaemia's. Defesral is administered parenterally and desferrioxamine mesilate (Hospira) is administered intramuscularly, intravenously, or subcutaneously.

Deferasirox

Deferasirox (Exjade, Novartis pharmaceuticals) is an iron-chelating agent that is given once daily as a suspension (usually in water or fruit juice). It has a UK marketing authorisation for the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells, i.e. ≥ 2 transfusions/month) in patients with beta thalassaemia major aged 6 years and older.

Deferasirox also has UK marketing authorisation for the treatment of chronic iron overload due to blood transfusions when desferrioxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with other anaemias,

- in patients aged 2 to 5 years,

- in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).

Deferiprone

Deferiprone (Ferriprox, Apotex) is an iron chelator that is usually given 3 times daily as film coated tablets or as an oral solution. It has a UK marketing authorisation for the treatment of iron overload in patients with thalassaemia major when desferrioxamine therapy is contraindicated or inadequate.

Intervention(s)	Desferrioxamine Deferasirox Deferiprone
Population(s)	People with thalassaemia major who have developed chronic iron overload following blood transfusions
Comparators	Deferasirox, deferiprone and desferrioxamine will be compared with each other as appropriate

Outcomes	The outcome measures to be considered include:
	• liver iron content
	• total body iron excretion
	• cardiac iron content and cardiac function
	• serum ferritin levels, including:
	  ○ maintenance of iron balance
	  ○ induction of negative iron balance
	• mortality
	• adverse effects of treatment
	• health related quality of life

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the marketing authorisations. Where the evidence allows, combinations of the different iron chelators will be considered. Where appropriate, treatment of children and adults will be considered separately. If the evidence allows, the effect of adherence to treatment on outcomes will be considered.
Related NICE recommendations	None

Questions for consultation

Is the population defined appropriately or should it be limited to beta thalassaemia major?

What combination therapy should be included, and how should this be defined?

Are the subgroups suggested in 'other consideration's appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? For example, should patients with cardiac iron be considered separately?

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider desferrioxamine, deferiprone and deferasirox to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of desferrioxamine, deferiprone and deferasirox can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.