Iron chelation therapy for iron overload

Subject: Iron chelation therapy for iron overload
Policy Number: N/A
Ratified By: Clinical Guidelines Committee
Date Ratified: October 2012, reviewed October 2015, reviewed Feb 2019
Version: 1.3
Policy Executive Owner: Clinical Director, EIM ICSU
Designation of Author: Dr Farrukh Shah, Dr Sara Trompeter, Professor John Porter, Dr Bernard Davis
Name of Assurance Committee: Haemoglobinopathy MDT
Date Issued: February 2019
Review Date: 3 years hence
Target Audience: Haematology thalassaemia unit and pharmacy department
Key Words: Iron overload, thalassaemia, chelation, desferrioxamine, deferiprone, deferasirox
### Version Control Sheet

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author</th>
<th>Status</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10/2012</td>
<td>Farrukh sh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>10/2014</td>
<td>Farrukh Shah</td>
<td>Update monitoring and treatment</td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>02/2019</td>
<td></td>
<td></td>
<td>Updated new doses of chelators</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Updated indications as per NHSE policy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Updated role of combination therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Updated frequency of monitoring using MRI as per NHSE policy</td>
</tr>
</tbody>
</table>

Iron chelation therapy for iron overload, Dr Farrukh Shah version 1.3
desferrioxamine, deferasirox, deferiprone, iron overload

Criteria for use

This document provides practice guidelines to assist medical, nursing and pharmacy staff to ensure the effective and safe management of patients with chronic iron overload.

Iron overload may result from repeated blood transfusion in patients with transfusion dependant thalassaemia, Sickle cell anaemia, or rarer anaemias that either require regular transfusion or intermittent transfusion such as Diamond Blackfen Anaemia (DBA), Congenital Dyserthropyoietic anaemia (CDA), Congenital Siderblastic anaemia (CSA),Pyruvate Kinase Deficiency and other rarer anaemias. Alternatively patients can develop iron overload where there is a genetic predisposition to accumulate iron such as non-transfusion dependant thalassaemia or genetic haemochromatosis.

The effects of iron overload are serious and can be life threatening. There is no natural system to rid the body of excess iron thus it is imperative that such patients have their iron removed. There are two ways of doing this: chemically using chelation agents and physically using venesection. Chelation is what is needed in anaemic patients, venesection can be used in people with genetic haemochromatosis and in those people whose transfusion dependant anaemia has been cured e.g. following a bone marrow transplant.

Chelation can also be used in groups where venesection is normally recommended as adjuvant therapy or where venesection in these groups cannot be tolerated. Venesection will not be covered in this guideline

If a patient is admitted with iron overload related problems it is essential that Dr Shah, Dr Drasar or Dr Davis are contacted as a matter of urgency.

For routine issues around setting up and managing desferrioxamine chelation please contact the thalassaemia unit.

Background

The risks of transfusional iron overload result from the abnormal quantity and distribution of iron into target tissues that include liver, heart, pancreas, anterior pituitary, thyroid, parathyroid glands. Here, uncoordinated labile iron generates free radicals and damages tissues, often irreversibly. Iron derived from the breakdown of transfused red cells first accumulates in macrophages of the liver, spleen and bone marrow and later spreads to liver hepatocytes, resulting in fibrosis and liver dysfunction in the short term, and ultimately cirrhosis and hepatocellular carcinoma in the long term.

Iron deposition in the endocrine tissues damages the pancreas causing diabetes, the thyroid causing hypothyroidism, the parathyroid causing hypoparathyroidism, the anterior pituitary causing poor growth and sexual development. It is early irreversible
damage to the pituitary that causes failure of sexual development, infertility and poor growth.

Iron deposition in the heart causes ventricular failure and arrhythmias. Although iron in accumulates in the liver before it spreads to the heart and endocrine tissues, it is this extra-hepatic spread that is responsible for early death and morbidity in thalassaemia.

Before the introduction of chelation therapy, death from heart failure in thalassaemia major patients was usual in their teens or early twenties. Heart failure remains the commonest cause of iron-mediated mortality. There is increasing concern for those who have had multiple adhoc transfusions in sickle cell disease carry a significant unrecognised iron burden and as they age put themselves at risk of the complications of iron overload in particular chronic liver disease and cirrhosis.

Chelation therapy with desferrioxamine has decreased mortality from heart failure from 6.3% at the age of 20 years in thalassaemic patients born from 1970-74, to only 1% in cohorts born after 1980, when subcutaneous desferrioxamine became available (Borgna-Pignatti et al., 2004). From studies in the pre-chelation era at post mortem (Buja and Roberts, 1971) and later using MRI (Jensen et al., 2003a), mainly in patients with MDS, it is clear that iron begins to spread into the heart after about 50 units of transfused blood in adults, being present in 100% of patients after 200 units of transfused blood. The reason for continued deaths in transfusional iron overload is due to poor compliance by the patients and/or inadequate dosing by their health providers of with chelation therapy. In particular there is often a lack of recognition of the existence or severity of iron overload and insufficiently aggressive prescribing by health providers where good control may well need more than one chelator. Poor compliance may result from treatment being started too late, being given with insufficient frequency or dosage or because of inadequate monitoring, psychological support or treatment modification. Whilst chelation may seem an expensive option, inadequate chelation is a far more costly proposition resulting in morbidity and protracted hospital admissions. Chelation therapy ideally aims to prevent iron deposition in the heart and endocrine tissues, rather than to attempt to remove iron from these tissues after the event because of poor management.

These guidelines have been written in reference to the following documents and guidelines:

1. Standards for the Clinical care of Adults with Sickle cell disease in the UK (Society, 2018)
2. Sickle Cell Disease in Childhood: Standards and guidelines for clinical care (programmes, 2010)
3. British committee for standards in haematology: Guidelines on the
4. Diagnosis and therapy of genetic haemochromatosis (review and update) (Fitzsimmons et al BJH 2017)
5. Thalassaemia international Federation (TIF) Guidelines for Clinical Management of Thalassaemia (TIF,3rd edition 2014)
6. Thalassaemia International Federation (TIF) Guidelines for management of non transfusion dependent thalassaemia NTDT 2nd edition 2017
8. Standards for the clinical care of children and adults with thalassaemia in the UK (Society, 2016)
9. NHS England clinical commissioning policy: treatment of iron overload for transfused and non-transfused patients with chronic inherited anemias: 16070/P

➢ Rationale for and goals of chelation therapy

PREVENTION:
This is done by maintaining iron balance and “safe” tissue iron levels by appropriately
   a) matching transfused iron with chelated (excreted) iron
   b) keeping ferritin and liver iron within target levels by regular monitoring
   c) appropriate catch-up of missed treatment periods especially with desferrioxamine

1) RESCUE
If prevention fails because due to inadequate or infrequent dosing or prescribing of chelation therapy by the patient or the doctor, then higher doses of chelation agents can be used to rescue patients by:
   a) by removing excess iron – this is a slow process taking several years because chelatable iron pools are finite at any moment in time
   b) reverse dysfunction (can work for heart rapidly in some cases but not other tissues)

➢ Specialist teams and appointments for those with iron overload

Cardiac MRI
There are two routes for scanning
   • Local Whittington hospital Cardiac T2*
   • UCLH detailed cardiac T2*

Cardiac Magnetic Resonance imaging (CMR) is a safe, non-invasive technique for assessing heart structure and function. CMR is able to answer many of the clinical questions previously unanswerable despite the use of multiple tests, as well as providing new information to guide clinical management. It is the gold standard for the monitoring of iron in the heart (T2*).

UCLH Cardiac T2*

Indications for this scan are:
   • Patient known to have cardiac iron already
• Patient has cardiac dysfunction and further information on heart function required

This is requested by contacting Dr James Moon at the Heart Hospital

<table>
<thead>
<tr>
<th>Cardiac MRI and Ferriscan</th>
<th>Dr James Moon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consultant Cardiologist</td>
</tr>
<tr>
<td></td>
<td>PA: Sandy Gardner</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:Sandy.gardner@uclh.nhs.uk">Sandy.gardner@uclh.nhs.uk</a></td>
</tr>
<tr>
<td></td>
<td>The Heart Hospital</td>
</tr>
<tr>
<td></td>
<td>18 Westmoreland St, London W1G 8PH</td>
</tr>
<tr>
<td></td>
<td>020 3456 3081</td>
</tr>
</tbody>
</table>

Whittington hospital Cardiac T2*

This is done at the Whittington hospital and requested on Sunquest ICE. This scan is analysed by resonance health and additional information about cardiac function is not available on this scan.

**Cardiac T2* cut off values are:**
T2*>20ms no myocardial iron overload
T2*<20 ms >8 ms mild to moderate myocardial iron loading
T2*<8ms severe myocardial iron loading

**Frequency of scanning:**
Patients with cardiac iron overload: annually if T2>8ms and <20 ms
Six monthly if T2*<8 ms
Patients with no cardiac iron loading but severe hepatic iron overload: annual
Patients with no cardiac or hepatic iron overload: cardiac T2* scan assessments can be done every 2 to 4 yearly depending on patients compliance to iron chelation and their ferritin trends

**AT ANY POINT A LOW EJECTION FRACTION IS A SIGN OF SERIOUS CONCERN REGARDLESS OF THE ABSOLUTE T2* VALUE**

**Ferriscan**
The MRI machine can also be calibrated to accurately measure iron in the liver (R2) known as a "ferriscan". This is the gold standard for the monitoring of iron in the liver. This is performed at the Whittington Hospital and can be requested on Sunquest ICE. Reports generally are back in 48 hours and can be requested from Haematology secretaries.

**Frequency of scanning:**
Annually for all patients unless on intensive chelation regime and rapidly falling ferritin in which case it can be undertaken at 6 monthly interval if needed.

**Cardiac Echo and Specialist Cardiology**
Dr Malcolm Walker is the cardiologist with an interest in myocardial iron overload. He runs a one-stop clinic where patients can have their echo and be reviewed by the consultant at the same appointment. All patients are reviewed on a yearly basis if they have cardiac iron overload or cardiac dysfunction.

Those who have no cardiac problems will be seen at longer intervals depending on other underlying conditions after discussion with Dr Walker.

Referrals can be made using the standard referral template. Clinical information should include: diagnosis, complications, medication and transfusion programme.

<table>
<thead>
<tr>
<th>Specialised Cardiology</th>
<th>Dr Malcolm Walker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consultant Cardiologist</td>
</tr>
<tr>
<td></td>
<td>PA: 020 3447 9951</td>
</tr>
<tr>
<td></td>
<td>The Hatter Cardiovascular Institute</td>
</tr>
<tr>
<td></td>
<td>67 Chenies Mews</td>
</tr>
<tr>
<td></td>
<td>London WC1E 6HX</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.hatter-cardiovascular-institute.co.uk/">http://www.hatter-cardiovascular-institute.co.uk/</a></td>
</tr>
</tbody>
</table>

Urgent ECHO can be done at Whittington hospital but requires liaison with the ECHO lab. It is important that routine monitoring ECHOs are only done by Dr Walker team as the expertise is essential for diagnosis of iron related cardiomyopathy.

Management of iron overload

Heart failure can be prevented with chelation therapy. Evidence shows that transfusional iron overload leads to an increased risk of iron deposition in the heart irrespective of the underlying disease process. This evidence comes from both post-mortem studies (2) and MRI studies (3).

Research at the UCLH/Whittington unit which has the largest experience in the UK, shows that 40-50% of TM patients have increased myocardial iron loading (T2* values < 20ms) about 40% of multi-transfused MDS patients, in excess of 70% of patients with Diamond-Blackfan Anaemia (DBA), and congenital sideroblastic anaemia. Sickle cell anaemia patients seem to be at less risk of cardiac iron overload but heart iron deposition still occurs and it as this population now moves into older age the sequelae of repeated adhoc transfusion is becoming more evident with an increasing awareness of chronic liver disease and cirrhosis in this patient group (4)

In prospectively designed studies, response of transfusional iron overload to chelation therapy the same with respect to iron balance and to patterns of ferritin response across a range of underlying diagnoses including thalassaemia major, myelodysplasia (MDS), (DBA), Aplastic Anaemia, Fanconi Anaemia, Pyruvate Kinase Deficiency, Congenital Sideroblastic Anaemia (5)

Unit policy therefore is that all forms of transfusional iron overload, where life expectancy from the underlying disease is in excess of the time taken for iron mediated tissue damage to result, merit chelation therapy unless iron removal by phlebotomy is appropriate.
Thalassaemia Intermedia, those with rarer anaemias such as Pyruvate Kinase deficiency and CSA can present with iron overload which can be severe and associated with considerable morbidity. These patients have chronic anaemia due to the underlying disorder and therefore need to be treated with iron chelation. This is funded via NHS England and the national iron chelation policy.

**When to start chelation therapy.**

Current guidelines across a range of conditions including, thalassaemia major, sickle cell disease and MDS, DBA, etc. recommend initiation of chelation therapy after 10-12 transfusion episodes or when serum ferritin reaches 1000µg/L in patients with an otherwise good prognosis (Bennett, 2008, Suzuki et al., 2008, (TIF), 2014) (Gattermann, 2008).

In patients who have developed iron overload but are not on regular blood transfusions and have anaemia secondary to the underlying disorder such as Thalassaemia Intermedia or rarer anaemias then iron chelation should be initiated. The drug and dose will be subject to a number of factors including severity of iron overload, underlying renal and liver disease.

It is not known whether chelation with deferiprone or deferasirox can be commenced at lower levels of transfusional iron loading so for the present, these starting recommendations are applied to all chelation regimes (6).

**What chelation therapy to use.**

**First line prevention chelation therapy for new patients who have never received chelation therapy:**

**In patients under the age of 2:**
- Desferrioxamine is recommended as first line at doses below 40mg/kg/day on 5 nights a week as 8-12 hour infusions.
- Deferasirox (off label use) in families where desferrioxamine has been attempted and parents have been unable to comply.

**In patients aged 2 and below 6 years.**
- desferrioxamine (Desferal,) 40mg/kg/day minimum 5 days a week as 8-12h sc infusions
- Deferasirox FCT 14-28 mg/kg/day once daily if the family has refused desferrioxamine infusions.

**In patients aged 6 and over**
- deferasirox (Film Coated Exjade) 14-28 mg/kg/day as a once daily dose.
- desferrioxamine (Desferal,) 40mg/kg/day minimum 5 days a week as 8-12h sc infusions.
In adults the desferrioxamine dose can be increased to 40-60mg/kg/day as 8 to 24 hour infusions sc depending on the severity of iron overload and patients ability to comply.

**Second line therapy**
In patients unwilling or unable to tolerate or comply with either desferrioxamine or deferasirox mono-therapy, or where control of iron load is inadequate, (ferritin consistently >2500µg/L or liver iron > 15mg/g dry wt).

- deferiprone mono-therapy (75-100mg/kg/day in three divided doses) with careful monitoring of hepatic iron
- Deferiprone and desferrioxamine (various regimens).
- deferasirox and desferrioxamine (selected cases failing other modalities)
- deferasirox and deferiprone (consultant decision only)

**Rescue therapy for patients with cardiac iron overload**

For patients with evidence of increased myocardial iron loading, irrespective of the level of serum ferritin or liver iron, intensification of therapy should be considered. The T2* values used for these guidelines are based on recently presented evidence about the impact of T2* prospectively on cardiac risk (7).

**T2* 8-20ms with normal heart function**
Consider the following options:

- Intensification of desferrioxamine dose and or frequency and /or switching from SC to IV
- Increasing dose of deferasirox FCT (21-28mg/kg/day)
- switch to deferiprone monotherapy, particularly if liver iron is well controlled
- Add deferiprone to desferrioxamine therapy. The optimal regimens will depend on individual patient: their age, their ability to comply with each chelation modality and the history of previous chelation therapy.
- Combined desferrioxamine and deferiprone if deferiprone is contraindicated
- Combined Deferasirox and deferiprone if monotherapy of either drug is insufficient to control iron burden and patient unwilling or unable to use desferrioxamine.

**T2* values <8ms and normal heart function**
Consider combination therapy with one of the following:

- desferrioxamine and deferiprone (exact regimen requires careful consideration)
- Deferoxamine and deferasirox (Aydinok, Kattamis et al. 2015)
- Deferasirox and deferiprone (Elalfy, Adly et al. 2015)

**Ventricular dysfunction** (fall in LVEF outside normal values) with myocardial iron loading (T2*<20ms).

- Consider 24h desferrioxamine continuous infusion preferably intravenously
- Intensive combination regime of desferrioxamine with oral deferiprone or an intensive combination regime of deferiprone and desferrioxamine.
• Desferioxamine and deferasirox combination (Aydinok, Kattamis et al. 2015)

Patients with clinical heart failure:

• Admit for intensive 24h IV desferrioxamine with or without deferiprone.

• On discharge from hospital continue on monotherapy with desferrioxamine intravenously 24/7 or combination therapy with desferrioxamine and deferiprone orally or if contraindicated then deferasirox if patient previously tolerated this for as long as central venous access is available

Please see Whittington Hospital NHS Trust Guideline: Management of acutely ill thalassaemia major patients

➢ Rationale and practicalities for monitoring of iron overload and response

The following recommendations for patients receiving regular long-term transfusion:

1) Iron loading rate from transfusion.

This is calculated by:

\[
\text{Number of units given over a year} \times 200 \\
\text{Patients weight (Kg) } \times 365
\]

Patients with average transfusion rate (0.3-0.5 mg/kg/day) will require average doses of iron chelation drugs.

Whereas those with transfusion rate less than 0.2 mg/kg/day or > 0.5 will require dose adjustment accordingly (8).

2) Serum ferritin

Serum ferritin broadly correlates with body iron loading and can be performed frequently and relatively inexpensively.

However serum ferritin also increases as a result of tissue damage and inflammation and is depressed by ascorbate deficiency (9)
The relationship between serum ferritin and iron stores is similar in thalassaemia major and sickle cell disease provided serum values are taken several weeks away from a vaso-occlusive sickle crisis but in thalassaemia intermedia, serum ferritin tends to underestimate the degree of iron overloading (10, 11).

TIF guidelines and the NHS England National iron chelation policy recommend chelation for patients with thalassaemia intermedia syndromes who are not transfused if the serum ferritin is above 800 ug/l.

Serum ferritin has also been used as a way of modifying the dose of chelation treatment, based on experience with desferrioxamine therapy where desferrioxamine mediated toxicity is more likely in the context of low serum ferritin levels.

Long-term control of serum ferritin, (at least with desferrioxamine therapy) has prognostic significance.

If the ferritin is maintained below 2500µg/L (with desferrioxamine) on a long term basis this is associated with a significantly lower risk of iron mediated cardiac disease and death (12) (13) (14) (1).

Maintenance of an even lower serum ferritin of 1000µg/L may be associated with additional advantages (12)

- Calculation of the therapeutic index is important with desferrioxamine (15):

  \[
  \frac{\text{Mg/kg/day of desferrioxamine (over 7 days)}}{\text{Serum ferritin}} = < 0.025
  \]

  With deferasirox, dose reduction is recommended if there is a clear falling trend towards 500µg/L

  With deferiprone once the ferritin is below 500ug/l then the dose is reduced to between 50-75mg/kg/day in 3 divided doses

3) Liver iron concentration (LIC) yearly by ferriscan:

LIC relates to body iron stores in a well-defined relationship namely (16):

\[
\text{body Iron stores in mg/kg} = 10.6 \times \text{the LIC (in mg/g dry wt)}
\]

This is not affected by the problems seen with ferritin. Normal LIC values are up to 1.8mg/g dry wt and levels up to 7mg/g dry wt are seen in some non-thalassaemic populations without apparent adverse effects.

Sustained high LIC values (greater than about 15-20mg/g dry wt) over a period of time predict an increased risk of liver fibrosis progression and of liver function abnormalities (17, 18)

In unchelated patients, similar LIC values predict an increased risk of myocardial iron deposition and to iron induced cardiomyopathy(2)
Intensive chelation therapy reduces liver iron faster than heart iron so that a simple relationship between LIC and estimated heart iron values are often not seen once long term or intensive chelation therapy has been used (19). Thus patients may develop heart failure after iron has been removed from the liver but while excess concentrations are found in the heart.

4) Heart iron and function

Iron mediated cardio-myopathy remains the commonest cause of death in thalassemia major and myocardial iron loading clearly occurs in other forms of transfusional iron overload. Identification of patients at the greatest risk, so that effective intensification of therapy can be introduced, is a key goal in the monitoring of patients with transfusional iron overload (12, 19).

5) Long term quantitative sequential measurement of LVEF has shown that a fall in ejection fraction below reference values for the method used indicated 35 fold increased risk of cardiac failure and death with a median interval to progression of 3.5 years in thalassaemia major (1).

Longitudinal monitoring of heart function is now most conveniently and reproducibly obtained by MRI techniques.

The myocardial T2* is a gradient echo MRI method that is now the most widely used to estimate myocardial iron and has been found to be highly reproducible worldwide. The risk of developing heart failure in the next 12 months is directly related to the T2* values. Values <8ms have a particularly high risk. Cardiac MRI should be done at baseline and then according to iron burden assessments and clinical evidence of compliance/efficacy of chelation. In T2* is performed every couple of years or all patients but anyone with evidence of myocardial iron loading is done annually.

Dr Walker’s heart clinic yearly operates a dedicated weekly clinic for patients with haemoglobinopathies and/or transfusional iron overload. Here echocardiography is performed and additional cardiological tests organised as necessary. In addition to screening for iron-mediated cardiomyopathy, pulmonary hypertension screening by echocardiography is undertaken.

Monitoring for other clinical effects of iron overload:

The earliest consequence of iron overload to manifest itself in transfused children is hypogonadotrophic-hypogonadism, which although not fatal, has severe consequences for growth, sexual development, fertility and osteoporosis (20).

Close regular monitoring for the cardiological, endocrinological, growth and developmental effects of iron overload is an essential part of management of iron overload.
Use of monitoring to identify patients at the highest risk from transfusional overload

N.B. These are patients who by definition have failed prevention treatment and are likely to require treatment intensification.

The primary goal of chelation therapy is to prevent patients reaching the following high-risk criteria:

1) High sustained levels of serum ferritin (>2500µg/l):
   Patients who over several years spend most of their time with ferritin values above this value are at increased risk of extra-hepatic damage and heart failure as shown in several studies (12)

2) Liver iron consistently > 15mg/g dry wt.
   The risk of heart disease is greater if body iron and hence liver iron is not controlled. Liver dysfunction is also more likely as well as progression to cirrhosis. A single cross sectional measure of LIC will not predict heart disease however as intensive chelation decrease LIC can rapidly while removing heart iron only slowly (21).

3) Decreased myocardial T2*
   This reflects increased iron in the heart as measured using MRI by T2*. Low T2* values lead to an increased risk of heart failure in a manner that is proportional to the shortening of the T2*.

   Values between 10-20 ms are associated with a higher risk of decreased left ventricular function than patients with normal T2* values (>20 ms) very small risk of heart failure.
   Patients with T2* values of 8-10 ms have about a 12% risk of developing heart failure in the next year:
   Patients with T2* values of 6-8 ms have a 30% chance of developing heart failure in the next year and patients with T2* values < 6 ms have a 50% chance of developing heart failure in the next year.

   Chelation therapy strategies should reflect these relative risks.

4) Decrease left ventricular ejection fraction.
   This is a relatively late event but identifies patients with a 35 x increased risk of developing heart failure in the next two years.
   Once this has developed, intensive 24h chelation is recommended with desferrioxamine with or without deferiprone.

➤ Chelation dosing and monitoring
As there is a fine balance between iron accumulation and iron depletion, choice of the correct chelator and dosage is done on a case by case basis; is tailored to the current and previous clinical situation and monitoring results; and is critical to outcome.

Decisions to commence alter or stop chelation MUST be made by a consultant. If there are any issues regarding chelation these issues MUST be discussed with the consultant.

Patients are usually defined as having chronic iron overload if their ferritin level is over 1000ug/l though it should be noted that patients may have lower ferritins and significant iron overload. This is particularly though not uniquely the case in those who have recently started an aggressive regimen having previously been underchelated. Here the ferritin drops prior to the movement of the iron from the organs.

**Deferasirox FCT**
(Refer to www.medicines.org.uk for most up to date licensed information)

a) patients with beta thalassaemia major aged 2 years and over.

b) Chronic iron overload due to blood transfusion when deferoxamine therapy is contraindicated or inadequate in the following patient groups:

- in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) 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) aged 2 years and older,

- in patients with other transfusion dependent anaemias aged 2 years and older

**Dose**
Commence at 14mg/kg/day, taken regularly once daily. If patients are already excessively iron loaded and the goal is to decrease the iron load (LIC) or serum ferritin, then doses up to 21-28 mg/kg/day are recommended. For patients with myocardial iron loading, doses up to 28mg/kg/day have been given successfully in clinical trials.

**Tablet Size**
All doses should be prescribed to the nearest tablet size. The tablet sizes available are 90mg, 180mg and 360mg.
**Method of administration**

Deferasirox should be taken with a light meal or an empty stomach, preferably at the same time each day.

For children the tablets can be crushed and added to yoghurt or applesauce or similar product and administered.

**Dose alterations (see www.medicines.org.uk for full guidance)**

**Dose alterations due to response**

- It is recommended that serum ferritin be monitored every 4 to 12 weekly and that the dose of Deferasirox be adjusted, if necessary, every 3 to 6 months based on the trends in serum ferritin. Dose adjustments may be made in steps of 3.5 to 7 mg/kg and are to be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden). Maximum dose 28mg/kg/day.
- In patients whose serum ferritin level has reached the target, dose reductions in steps of 3.5 to 7 mg/kg should be considered to maintain serum ferritin levels within the target range.
- If serum ferritin falls consistently below 500 µg/l, in transfusion dependent patients reduction of treatment should be considered.
- In patients who developed iron overload due to previous transfusions and are no longer transfused or are currently on automated apheresis with an iron neutral or iron reducing exchange then chelation therapy should be stopped.
- In patients with NTDT a ferritin of 500 cannot be used as a marker of effective chelation and if the ferritin is on a continuous downward trend then a ferriscan liver iron should be organized to confirm iron burden goal is achieved prior to stopping chelation.

**Dose alterations due to renal impairment**

1. For adult patients, the daily dose may be reduced by 7 mg/kg if a rise in serum creatinine by >33% above the average of the pre-treatment measurements and estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) are seen at two consecutive visits. For paediatric patients, the dose may be reduced by 7 mg/kg if estimated creatinine clearance decreases below the lower limit of the normal range (<90 ml/min) and/or serum creatinine levels rise above the age-appropriate upper limit of normal at two consecutive visits.

2. After a dose reduction, for adult and paediatric patients, treatment should be interrupted if a rise in serum creatinine >33% above the average of the pre-treatment measurements is observed and/or the calculated creatinine clearance falls below the lower limit of the normal range.

3. Treatment may be reinitiated depending on the individual clinical circumstances.
4. Refer to renal team if persistently raised creatinine.

**Dose alterations due to hepatic impairment**

Deferasirox is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50%, and it must be used with caution in such patients.

Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month. It is recommended that serum transaminases, bilirubin and alkaline phosphatase be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels **>5 times upper limit of normal that cannot be attributed to other causes, deferasirox should be interrupted**. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

**Contra-indications & Precautions**

Deferasirox can be used with caution and careful monitoring in patients with estimated creatinine clearance <60ml/min. These patients must be discussed with the haemoglobinopathy consultant in charge of their care.

It should not be used in patients with creatinine clearance <30ml/min unless a consultant from the haemoglobinopathy team approves it use. Much lower doses are required in this situation and more frequent monitoring. This should be a rare event on a case by case basis with multi-disciplinary discussion.

If a patient is on dialysis then deferasirox can be used at standard doses.

Renal function should be estimated using the Cockcroft and Gault formula, and not the eGFR values

**Cockcroft and Gault formula**

Creatinine clearance (ml/min) = \( F \times (140 - \text{age}) \times \text{weight in kg} / \text{serum creatinine umol/l} \),

Where \( F = 1.04 \) for females, \( 1.23 \) for males

Deferasirox may be used in combination with other iron chelators though this must be initiated by a consultant haematologist.

**Side Effects**

Nausea vomiting and diarrhoea are the primary side effects in general these are managed by changing the timing of the medication, taking it with food or last thing at night helps resolve the majority of these. In patients with persistent diarrhoea it is
mostly likely due to lactose intolerance and lactase can be used to help alleviate this
( not available in BNF; must be purchased from health food shops)
Mild to moderate skin rashes occur in 7% of patients temporary dose reductions
followed by subsequent return to the therapeutic dose are all that is required.
Severe skin rash: Occurs in <1% of patients Dose interruption followed by
permanent cessation or gradual reintroduction at a smaller dose. Severe skin rashes
can sometimes be managed by using 10mg of prednisolone daily starting 2 days
before re-challenging with deferasirox. The initiation dose should be 90mg in children
and 180mg in adults. The dose should then be kept at this level for a week, if the
rash does not re-occur then gradual dose escalation with the target dose being
achieved in 4 weeks. The prednisolone can then be reduced over the course of a
fortnight.
Angio-oedema is a very rare side effect and in this case deferasirox must be
stopped.
Other effects such as deafness, neurosensory deafness or hypoacusis were
reported as adverse events irrespective of drug relationship in thalassemia major
patients in the 1 year core trial in eight patients on deferasirox compared with seven
on desferrioxamine(22). Cataracts or lenticular opacities were reported as adverse
events irrespective of drug relationship in two patients on deferasirox and five on
desferrioxamine. Overall the tolerability profile compared favourably with
desferrioxamine in this study. The results of the 4 year extension will be useful in
interpreting the significance of these findings. No drug-related agranulocytosis were
observed in thalassemia or sickle patients from the core studies.

Desferrioxamine
(Refer to www.medicines.org.uk for most up to date licensed information)

**Indications**

Iron overload - acute iron poisoning; primary and secondary haemochromatosis
including thalassaemia and transfusional haemosiderosis; in patients in whom
concomitant disorders (e.g. 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
anaemias.

**Dose**

Starting dose is 40 mg/kg/day as a subcutaneous infusion over 8 - 12 hours.

Ideally desferrioxamine should be given daily. However, if the patient is well it may
be more appropriate to give 7 days treatment over 5 days.

**Example**

A patient who weighs 60kg; their dose is 60x40 = 2400mg
The total cumulative weekly dose is 2400x7 = 16800mg
This dose over 5 days is 16800/5 = 3360mg
Desferrioxamine can be delivered using a syringe driver, however more recently balloon infusors are used. These are prescribed through “Healthcare @ Home” and are delivered to the patient’s house.

Standard dosing for children is ≤ 40mg/kg/day given as a 8-12h infusion on a minimum of 5 nights a week. This is the minimum frequency associated with good long-term survival.

**Method of administration**

Desferrioxamine is administered subcutaneously in a 8 or 12 hour infusion by means of a portable, light-weight, infusion pump which, under usual circumstances, is delivered on a fortnightly basis to the patient by Healthcare at Home. In patients with severe cardiac iron overload, it may be desirable to have a continuous infusion and it may be preferable to have this administered intravenously. This will be a consultant decision.

For those patient who are not receiving their infusions in the premade infusors, vials come in 500mg and 2g of desferrioxamine and it is reconstituted in water for injection. Information regarding reconstitution can be found on [www.medicines.org.uk](http://www.medicines.org.uk).

Patients should be treated 4-7 times a week depending on the degree of iron overload. Continuous intravenous infusion is recommended for patients incapable of continuing subcutaneous infusions and in those who have cardiac problems secondary to iron overload. Implanted intravenous systems can be used when intensive chelation is carried out at home.

**Dose alterations**

Recent prospective trials show that doses of 35-50mg/kg, 5 nights a week, will achieve negative iron balance in 75% of patients receiving transfusions at an iron loading rate of 0.3-0.5 mg/kg/day (8).

For patients receiving high transfusion rates (an iron loading rate of > 0.5mg/g/day), 52% of patients will be in negative iron balance but this can be increased to 89% at doses >50mg/kg/day.

Doses >60mg/kg/day are not recommended because of risk of retinal and audiometric toxicity. At doses inducing a clear negative iron balance (progressive fall in LIC or ferritin), the dose needs to be adjusted downwards as the ferritin falls: the therapeutic index can be used as a guideline under these circumstances (23).

For patients at high risk of heart failure, 24h treatment is recommended if desferrioxamine is to be used if heart function is affected with or without deferiprone.

**Contra-indications & Precautions**

Desferrioxamine should not be given to pregnant women unless in the judgement of the physician, the expected benefits to the mother outweigh the potential risk to the child. This particularly applies to the first trimester. If a patient becomes pregnant,
the consultant should be informed immediately. Desferrioxamine should not be used in combination with prochlorperazine (a phenothiazine derivative) since prolonged unconsciousness may result.

Caution is advised when desferrioxamine mesilate is used in combination with any phenothiazine. Gallium$^{67}$ imaging results may be distorted because of the rapid urinary excretion of desferrioxamine-bound radiolabel. Discontinuation of desferrioxamine 48 hours prior to scintigraphy is advised. Desferrioxamine should be used with caution in patients with renal impairment since the metal complexes are excreted via the kidneys. Hypersensitivity to desferrioxamine is a contraindication unless the patient can be desensitised (see desensitisation regimen Appendix10).

**Monitoring for efficacy and side effects**

Most of the toxic effects of desferrioxamine are dose related; effects on growth, skeletal changes, audiometric and retinopathic effects are more likely at higher doses of the drug: these toxicities are rare in thalassemia major at doses ≤ 40 mg/kg/day.

**Side Effects**

**Injection Site Reactions:**
Generally local mild reactions may occur with skin reddening and soreness at the site of subcutaneous infusions. These are often caused by desferrioxamine being reconstituted above the recommended concentration of 10%. Increasing the volume of water used to dilute the desferrioxamine can substantially decrease reactions. On occasions when local reactions remain a problem, the addition of a small dose of hydrocortisone (5-10mg) to the desferrioxamine solution may be effective. This can be done by Healthcare at Home upon appropriate alteration of the prescription.

**Retinal Toxicity:**
Retinal and optic nerve disturbances sometimes associated with pigmentary retinal changes, were originally described at very high doses of desferrioxamine (125 mg/kg/day) and are rare at currently recommended doses. Other abnormalities include blurred vision, loss of central vision, night blindness and optic neuropathy. The risk may be higher in patients with diabetes or other factors affecting the blood-retinal barrier. Electroretinography is performed at Moorfields eye hospital yearly in patients new to treatment, in patients on intensive or combination therapy, or with ferritin values falling. Abnormalities require careful consideration about interrupting or reducing therapy.

**Auditory toxicity:** High frequency sensorineural hearing loss was initially described in about a quarter of well-chelated patients. The risk is greatest in patients with low degrees of iron overload receiving high doses of desferrioxamine. This complication may be reversible if diagnosed early and reducing the dose and by keeping the therapeutic index (ratio of dose in mg/kg/day divided by the serum ferritin) below 0.025 and by monitoring audiometry regularly, the risks can be
minimized. It is advisable to perform audiometry before starting treatment then about once a year.

**Effects on Growth and Bone.**
Desferrioxamine usually improves growth in thalassemia major by decreasing iron overload but if too much is given, growth retardation may result. The risk factors are young age (< 3 years at commencement of treatment), higher doses of desferrioxamine and lower levels of iron overload. Rickets-like bony abnormalities have been described in association with decreased growth and radiographic abnormalities of the distal ulnar, radial and tibial metaphases. Vertebral growth retardation or vertebral demineralisation and flatness of vertebral bodies may occur in well chelated patients (14, 24).
It is advisable to monitor height velocity as well as sitting and standing height twice yearly and adjust dosing as necessary. A quick resumption in growth follows reduction in desferrioxamine dosing without the need to stop treatment (25).
Periodic surveillance on growth and on bone are recommended with attention to the sitting and standing heights. Radiologic assessment of the thoracolumbar-sacral spine as well as the forearm and knees is recommended in patients with growth disturbances or changes in ratio of sitting to standing height. Dose reduction should be considered if significant changes are noted.

**Generalized reactions:** such as fever, muscle aches and arthralgia occur rarely. True systemic allergic reactions are uncommon but can include anaphylaxis. Some patients can be successfully desensitized using published procedures to prevent further allergic reactions.

**Renal impairment:** characterized by a reduction in the glomerular filtration rate, has been reported in occasional patients given high doses of desferrioxamine and clinically significant but reversible decrease in GFR in 40%.
**Lens opacities:** Observed rarely in patients receiving high doses of desferrioxamine. Improved when the chelator was withdrawn.

**Patients who present with diarrhoea, abdominal pain or fever should stop desferrioxamine until Yersinia infection can be reasonably excluded.**

If Yersinia infection is proven or seriously suspected, desferrioxamine should be withheld until the infection has been eliminated by antibiotic treatment. Prolonged treatment with an antibiotic such as ciprofloxacin is occasionally necessary. In any patient with undiagnosed fever it is wise to consider stopping the desferrioxamine until the cause is identified.

**Deferiprone**  
(Refer to www.medicines.org.uk for most up to date licensed information)

**Indications**
Deferiprone is indicated for the treatment of iron overload in patients with thalassaemia major when desferrioxamine therapy is contraindicated or inadequate

**Dose**
Most studies have used 75mg/kg/day in three divided doses and this is the standard recommended dosing. Dose per kilogram body weight should be calculated to the nearest half tablet. See table below for recommended doses for body weights at 10 kg increments.

A higher dose close to 100mg/kg/day has been subject to randomised testing in 27 patients showed a small decrease in LIC (0.9mg/g dry wt). LVEF improved within the normal range more with deferiprone than desferrioxamine(26).

Current labelling in the EU allows doses up to this value.

**Method of administration**

**Available as 500mg or 1000mg tablets or 100mg/ml oral solution**

**Dose table**

To obtain a dose of about 75 mg/kg/day, use the number of tablets suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Total daily dose (mg)</th>
<th>Dose (mg, three times/day)</th>
<th>Number of tablets (three times/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1500</td>
<td>500</td>
<td>1.0</td>
</tr>
<tr>
<td>30</td>
<td>2250</td>
<td>750</td>
<td>1.5</td>
</tr>
<tr>
<td>40</td>
<td>3000</td>
<td>1000</td>
<td>2.0</td>
</tr>
<tr>
<td>50</td>
<td>3750</td>
<td>1250</td>
<td>2.5</td>
</tr>
<tr>
<td>60</td>
<td>4500</td>
<td>1500</td>
<td>3.0</td>
</tr>
<tr>
<td>70</td>
<td>5250</td>
<td>1750</td>
<td>3.5</td>
</tr>
<tr>
<td>80</td>
<td>6000</td>
<td>2000</td>
<td>4.0</td>
</tr>
<tr>
<td>90</td>
<td>6750</td>
<td>2250</td>
<td>4.5</td>
</tr>
</tbody>
</table>

A total daily dose above 100 mg/kg body weight is not recommended because of the potentially increased risk of adverse reactions.

**Dose alterations**

The effect of deferiprone in decreasing the body iron is directly influenced by the dose and the degree of iron overload. After starting deferiprone therapy, it is recommended that serum ferritin concentrations be monitored every three months to assess the long-term effectiveness of the chelation regimen in controlling the body iron overload.
iron load. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Dose reduction should be considered once the ferritin falls below 500ug/l.

Contra-indications & Precautions

Hypersensitivity to the active substance or to any of the excipients. History of recurrent episodes of neutropenia.

There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy. Due to the clastogenic and teratogenic properties of the medicinal product. These women should be advised to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant. (27)

It is not known whether deferiprone is excreted in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone must not be used by breast-feeding mothers. If treatment is unavoidable, breast-feeding must be stopped. Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis.

Monitoring for efficacy and side effects

Side Effects

The relationship of the key unwanted effects of agranulocytosis, neutropenia, arthropathy and fluctuations in LFT to dosing and to levels of iron loading have not been subject to prospective study, so that evidence based recommendations about dose reduction with these effects cannot be made. Neurological effects have been seen with accidental overdosing and are clearly dose related. Overall tolerability up to 4 years has been studied prospectively in a study of 187 thalassaemia major patients where the overall dropout rate increased from 15% after 1 year to 55% at 4 years.

Gastrointestinal effects: Nausea and/or vomiting were relatively common in the first year of therapy occurring in 24% of patients, with abdominal pain in 14%. Often settles without intervention. Consider switching therapy if symptoms persist. Starting with a low dose and gradual increases also help

Arthralgia and arthropathy: These vary greatly between studies, with the highest incidences 30-40% in the developing world and the lowest in Italy (<5%). Interrupt therapy if symptoms persist or progress

Fluctuation in liver function tests: These were reported in 44% of patients in a pooled analysis.

If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered if this is above 5 times upper limit of normal.
Neutropenia and agranulocytosis  Agranulocytosis was initially reported in 3-4% of patients treated with deferiprone, and mild neutropenia occurred in an additional 4%. Neutropenia may last from 4 to 124 days.

**Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia.** The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood (FBC) with differential immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly FBC and differential to be obtained for three consecutive weeks, to ensure that the patient recovers fully. Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed and an appropriate therapeutic regimen instituted.

**In the event of severe neutropenia or agranulocytosis:**
Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.
Limited information is available regarding rechallenge. Therefore, in the event of neutropenia, rechallenge is not recommended. In the event of agranulocytosis, rechallenge is contraindicated.

**Zinc deficiency**  Small mean decreases in plasma zinc and cases of zinc deficiency not requiring cessation of therapy have been reported. Consider oral zinc supplementation.

**Neurotoxicity**  Although not reported at conventional doses, overdosing has been associated with neurotoxicities. Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation. Interrupt therapy if neurological symptoms develop.

**Combined Deferiprone and Desferrioxamine**

**Indications**
By combining deferiprone with desferrioxamine, an increased proportion of patients may obtain iron balance and improved myocardial iron removal may be obtained compared with monotherapy with either of these drugs alone. In principle, there are an infinite number of dosing regimes to combine these two drugs but broadly these involve either simultaneous exposure or some way of alternating the drugs. If these chelators are present simultaneously in cells or in the circulation, they may interact by ‘shuttling’ iron from deferiprone onto desferrioxamine. Because both drugs have a short plasma half-life, if they are given sequentially, even in the same 24h period, there is limited opportunity for this interaction. The majority of clinical reports and studies have used some form of sequential therapy. The effects of simultaneous exposure on efficacy drug related side effects have not been compared formally in a prospective study.
Dose
Most studies have used standard dose deferiprone (75mg/kg/day in three divided doses during the day) with desferrioxamine given at night at standard doses (40mg/kg as an 8-12h infusion) between 2 and 5 times a week. Other studies use different frequency and dosing regimens. In general therefore, although data on iron balance are limited, the greater the frequency of desferrioxamine dosing, the greater the proportion of patients in negative iron balance so that in principle, the frequency of desferrioxamine dosing can be adjusted according to the perceived risk in the individual patient. This will be decided on a patient by patient basis after discussion with the consultant.

Side Effects
Formal safety data on combined treatment are limited. In general, alternating regimes are less likely to be an issue for toxicity compared regimes where chelation is simultaneous or overlapping.

Combinations of deferasirox with other chelators.
( these not commissioned by NHE iron chelation policy currently and are only prescribed on a case by case basis)

Indications
Experience with true combination (concomitant) therapy by prescribing deferasirox with another chelator has been reported in several studies. No evidence of untoward drug interactions or adverse effects have been reported.

Combination of dispersible deferasirox 20-30 mg/kg/day with desferrioxamine (30-15mg/kg 3-7 days/week) has been reported in a prospective trial (Lal A, et al. Blood. 2010;116:[abstract 4269] also Blood in press) and appears to effective and well tolerated in reducing both liver and myocardial iron, with additive effects on iron balance (Grady RW, et al. Blood. 2010;116:[abstract 5163]).

The combined used of deferiprone and deferasirox has been reported in case studies (Voskaridou et al., 2011) and in small series (Farmaki, et al. Blood Cells Mol Dis. 2011;47;33-40) as well a randomized clinical trial (Elalfy, Adly et al. 2015) achieving good control of body iron without reported side effects.

The use of such combination therapies should be reserved for patients in whom all monotherapies have failed to control liver or cardiac iron.

REFERENCES


NHS England clinical commissioning policy: treatment of iron overload for transfused and non-transfused patients with chronic inherited anemias: 16070/P

Elalfy MS, Adly AM, Wali Y, Tony S, Samir A, Elhenawy YI. Efficacy and safety of a novel combination of two oral chelators deferasirox/deferiprone over defereroxamine/deferiprone in severely iron overloaded young beta thalassemia major patients.


Fitzsimons et al; Diagnosis and therapy of genetic haemochromatosis (review and update) Br J Haematol. 2018 May;181(3):293-303.

Thalassaemia international Federation (TIF) Guidelines for Clinical Management of Thalassaemia ((TIF),3rd edition 2014)

Thalassaemia International Federation (TIF) Guidelines for management of non transfusion dependent thalassaemia NTDT 2nd edition 2017
Desferal Desensitisation Protocol

Prior to starting:

This process must be initiated by a consultant. The patient should give informed written consent

Day minus 1

Premedication starting 18 hours prior to desensitization:

- Methylprednisolone 40mg IV every 6 hours
  (or hydrocortisone 100mg every 6 hours as an alternative)
- Chlorphenamine 4mg PO every 6 hours

Day 0

Continue predmedication as per day minus 1

Desensitisation process

- Admit patient
  - to ITU for constant monitoring if previous anaphylaxis
  - To haematology ward or day care if minor allergy e.g. rash – discuss with Red Cell Consultant

- 6 separate infusions of increasing concentration are prepared for consecutive intravenous administration as below (should be ordered in advance from pharmacy)

- In the event of any grade 1 or more allergic reaction, stop the infusion and treat symptoms as necessary e.g. hydrocortisone, chlorphenamine, adrenaline etc. Restart the infusion once symptoms resolve

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Desferrioxamine dose</th>
<th>All doses are administered intravenously in 50ml 5% glucose over 30 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 micrograms</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>150 micrograms</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1500 micrograms</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15 mg</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>150 mg</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1500mg</td>
<td></td>
</tr>
</tbody>
</table>

then desferrioxamine 1500mg in 500mls saline IV infusion over 24 hours for 2-8 days (e.g. 4 days)
Day 1
Continue premedication as per day minus 1
Desferrioxamine 1500mg in 500mls saline IV infusion over 24 hours

Day 2-8 (max)
Desferrioxamine 1500mg in 500mls saline IV infusion over 24 hours

NB
- If successful and no reaction is present on completion of the desensitisation process, patients can continue on subcutaneous desferrioxamine daily at standard doses.
- The desensitisation process should NOT be interrupted. If interrupted, the chance of recurrence in allergy may increase.

Day 9 onwards
Gradually move towards the desired dose

Adapted from:
To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Yes/No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Does the procedural document affect one group less or more favourably than another on the basis of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethnic origins (including gypsies and travellers)</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nationality</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Religion or belief</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual orientation including lesbian, gay and bisexual people</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disability - learning disabilities, physical disability, sensory impairment and mental health problems</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Is there any evidence that some groups are affected differently?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Is the impact of the procedural document likely to be negative?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>If so can the impact be avoided?</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>What alternatives are there to achieving the procedural document without the impact?</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Can we reduce the impact by taking different action?</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
If you have identified a potential discriminatory impact of this procedural document, please refer it to the Director of Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact the Director of Human Resources.

**Checklist for the Review and Approval of Procedural Document**

To be completed and attached to any procedural document when submitted to the relevant committee for consideration and approval.

<table>
<thead>
<tr>
<th>Title of document being reviewed:</th>
<th>Yes/No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Title</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the title clear and unambiguous?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is it clear whether the document is a guideline, policy, protocol or standard?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2. Rationale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are reasons for development of the document stated?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3. Development Process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is it clear that the relevant people/groups have been involved in the development of the document?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Are people involved in the development?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is there evidence of consultation with stakeholders and users?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>4. Content</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the objective of the document clear?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is the target population clear and unambiguous?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Are the intended outcomes described?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5. Evidence Base</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are key references cited in full?</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Are supporting documents referenced?</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>6. Approval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title of document being reviewed:</td>
<td>Yes/No</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Does the document identify which committee/group will approve it?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>7. Dissemination and Implementation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there an outline/plan to identify how this will be done?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>8. Document Control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the document identify where it will be held?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>9. Process to Monitor Compliance and Effectiveness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are there measurable standards or KPIs to support the monitoring of compliance with and effectiveness of the document?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is there a plan to review or audit compliance with the document?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>10. Review Date</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the review date identified?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is the frequency of review identified? If so is it acceptable?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>11. Overall Responsibility for the Document</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**Executive Sponsor Approval**

If you approve the document, please sign and date it and forward to the author. Procedural documents will not be forwarded for ratification without Executive Sponsor Approval

<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
</tr>
</thead>
</table>

**Relevant Committee Approval**
The Director of Nursing and Patient Experience’s signature below confirms that this procedural document was ratified by the appropriate Governance Committee.

<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature</td>
<td></td>
</tr>
</tbody>
</table>

**Responsible Committee Approval – only applies to reviewed procedural documents with minor changes**

The Committee Chair’s signature below confirms that this procedural document was ratified by the responsible Committee.

<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Committee</td>
<td>Name &amp; role of Committee Chair</td>
</tr>
<tr>
<td>Signature</td>
<td></td>
</tr>
</tbody>
</table>
## Tool to Develop Monitoring Arrangements for Policies and guidelines

<table>
<thead>
<tr>
<th>Element to be monitored</th>
<th>Lead</th>
<th>Tool</th>
<th>Frequency</th>
<th>Reporting arrangements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor no of patients achieving target liver iron values</td>
<td>Dr Farrukh shah</td>
<td>Audit</td>
<td>Biannually</td>
<td>Pathology audit</td>
</tr>
<tr>
<td>Monitoring the number of patients developing new myocardial iron loading</td>
<td>As above</td>
<td>Audit</td>
<td>Biannually</td>
<td>As above</td>
</tr>
</tbody>
</table>