**BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)**

April 2015
Review Date: April 2018

**Bulletin 214: The use of iron chelator therapy for the management of iron overload in patients with Myelodysplastic syndromes (MDS)**

**JPC Recommendation:**

The committee agreed the following recommendation:

- The routine commissioning of iron chelator therapy for the management of iron overload in MDS is **not** supported.

---

**The Use of iron Chelator Therapy for the Management of Iron overload in Patients with Myelodysplastic Syndromes (MDS)**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>The use of iron chelator therapy for the treatment of iron overload in patients with Myelodysplastic syndromes (MDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Document status</td>
<td>Final</td>
</tr>
<tr>
<td>Date of last revision</td>
<td>7/4/15</td>
</tr>
<tr>
<td>Proposed Sector of prescribing</td>
<td>Secondary Care</td>
</tr>
</tbody>
</table>

**Introduction / Background**

The aim of this bulletin is to review the evidence of clinical and cost-effectiveness on the use of iron chelating therapy for the treatment of iron overload in patients with myelodysplastic syndromes (MDS) to enable the Bedfordshire & Luton Joint Prescribing Committee (JPC) to recommend to the CCGs (BCCG and LCCG) a local commissioning policy for the use of iron chelators in this patient group.

Iron chelating therapies are excluded from the national tariff. Until 31st March 2015, iron chelators were the commissioning responsibility of NHSE. (NHSE did not publish a commissioning policy on the use of iron chelators for the treatment of MDS) The use of iron chelators for many indications still falls under the remit of NHSE, however their use in the management of iron overload in patients with MDS has been transferred and is now a commissioning responsibility of individual Clinical Commissioning groups (CCGs). Prior to NHSE, PCTs had the commissioning responsibility for iron chelators and the policy( Bulletin 115, June 2009) stated: "There are limited data and the cost-effective case is less secure for the use of deferasirox in patients with myelodysplastic syndrome and so will not be routinely
The use of iron chelation therapy in the management of iron overload in MDS is currently an issue that is a cause for debate as this is an area where clinical trial evidence is lacking and experts acknowledge that there are several unanswered questions around the use of such therapy in this patient group. (1)

Background
The myelodysplastic syndromes (MDS) are a heterogenous group of malignant haematopoietic disorders characterised by dysplastic changes in one or more cell linages, ineffective haematopoiesis and a variable predilection to development of acute myeloid leukaemia (AML). The incidence of MDS is approximately 4/100,000 population / year, but it is predominately a disease of the elderly with an incidence of > 30/100,000 / year over the age of 70 years. (Extract from Ref. 1)

At diagnosis, all cases of MDS should be classified according to the WHO revised Classification 2008. Prognosis is largely based on the marrow blast percentage, number and extent of cytopenias and cytogenic abnormalities, which are grouped in a recently Revised International Prognostic Scoring System (IPSS/IPSS-R). Patients are classified as having lower risk MDS or a higher risk MDS.

For higher risk groups, drug treatment (e.g. azacitidine), intensive chemotherapy or haematopoietic stem cell transplantation is usually required. Low and intermediate risk MDS patients often only require supportive treatment including red blood cell transfusions for symptomatic anaemia. (1)

Lower Risk MDS Patients
Red cell transfusions are given primarily to correct symptomatic anaemia and improve quality of life (QOL). Chronic red cell transfusion will lead to complications including iron overload and the development of red cell alloantibodies. (1). Each unit of blood contains iron and as the human body has no physiological mechanism to actively excrete excess iron, repeated blood transfusions result in excessive accumulation of iron. Excess iron is deposited in various tissues in the body particularly the liver, heart and endocrine organs. This may lead to many complications including cardiomyopathy, liver cirrhosis, diabetes mellitus and reduced life expectancy.

- Licensing Information: Desferrioxamine - The relevant licensing indication applicable to MDS is: Desferrioxamine is licensed for the treatment of chronic iron overload e.g. Transfusional haemosiderosis in patients receiving regular transfusions e.g. thalassaemia major. Deferasirox - The relevant indication applicable to MDS is: For the treatment of iron overload due to blood transfusions when deferoxamine therapy is contra-indicated or inadequate in patients with other anaemias aged 2 years and older. Deferiprone is not licensed for use in MDS patients.
- The commissioning arrangements around the treatment of iron overload in patients with MDS has been transferred from NHSE to the individual Clinical Commissioning groups (CCGs). As iron chelators are excluded from the national tariff it is essential that a local commissioning policy is developed. Prior to NHSE, PCTs had the commissioning responsibility for iron chelators and the policy( Bulletin 115, June 2009) stated: “There are limited data and the cost-effective case is less secure for the use of deferasirox in patients with myelodysplastic syndrome and so will not be routinely funded by the PCTs. This will be reviewed as and when new information becomes available.”
- NHSE did not publish a commissioning policy relating to the use of iron...
chelators in MDS prior to the transfer of commissioning responsibility back to CCGs.

- Iron chelation is now made easier by the availability of oral iron chelators (especially deferasirox), in addition to the parenteral deferoxamine (desferrioxamine).
- Deferiprone, another oral iron chelator, is currently not approved for MDS, and can cause neutropenia in a small percentage of patients, a side-effect that is problematic in MDS.
- The use of iron chelation therapy in the management of iron overload in MDS patients is currently a cause for debate. Clinical trial evidence is lacking and experts acknowledge that there are several unanswered questions around the use of such therapy in this patient group.
- The efficacy data used for licensing of deferasirox was based on phase 2 studies comprising 47 MDS patients out of a total of 1009 (predominantly β-thalassaemia patients).
- A Cochrane review was undertaken and concluded ‘the benefits of deferasirox have not yet been established in RCTs. Several retrospective analyses and observational studies suggest a benefit with regard to certain outcomes (Excluded studies) (Porter 2004; List 2006, US3 study; Gattermann 2007, EPIC). However, the impact of iron chelation therapy with deferasirox on long-term outcomes or patient-relevant outcomes such as organ dysfunction or mortality has not been established in detail.’
- The Cochrane review reports that there is a randomised trial (TELESTO 2009) underway and that the results of this trial should help define the role of deferasirox and to establish clear indications for iron chelation in MDS.
- The Cochrane review also states that “the profile of adverse effects, which might be different for this patient group compared to people with thalassaemia urgently needs to be established to allow adequate balancing of the benefits and potential harms of iron chelation therapy for people with MDS.
- British Committee Standards in Haematology (BCSH) guidelines (Dec 2013) acknowledge that there is no direct evidence to support a survival benefit for iron chelation therapy in MDS and only randomised controlled trials will answer this definitively.
- Based on the available evidence, the British Committee Standards in Haematology (BCSH) Guidelines advise that iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload. However, consideration may be given to its use in certain circumstances. (NB: The BCSH guidelines also acknowledge that there is almost universal recommendation in national and international guidelines for iron chelation therapy in selected MDS patients (Greenberg et al 2011).
- If treatment is to be used, the BCSH guidelines state that desferrioxamine remains the therapy of choice with the longest record of safety and efficacy of all three agents available. Deferasirox is recommended for patients intolerant of desferrioxamine. Deferiprone could be considered in patients with normal baseline neutrophil counts.
- BCSH guidelines also state that patients treated with iron chelation therapy should ideally receive this treatment within clinical trials.
- An article published in Expert Review of Haematology (2013) states that retrospective data suggests that iron chelation therapy can improve survival in MDS, especially lower risk MDS, may reduce cardiac and hepatic complications, lead to haematological improvements and possibly decrease leukaemic transformation, infectious complications and transplant related mortality. The authors also state that the beneficial effects of iron chelation therapy on organ function and survival in MDS have yet to be demonstrated prospectively in a randomised fashion.
- The US food and Drug Administration (FDA) has added a black box warning for deferasirox for enhanced vigilance with renal impairment, hepatic impairment and gastrointestinal haemorrhage.
Scottish Medicines Consortium (SMC) recommendation (2007) states: – Deferasirox is not recommended for patients with myelodysplastic syndromes (this group were poorly represented in the clinical trial population and the economic case for this group of patients was not demonstrated.)

- Economic models have yet to be validated prospectively in clinical studies therefore the economic case has yet to be demonstrated in this group of patients.
- Average annual drug cost of treatment ranges from £4,700 to £12,800 for desferrioxamine (NB This is drug cost alone and does not include cost of infusion pumps , training required etc); £9,200 to £24,500 with deferasirox. Deferiprone is not licensed for MDS.

There are 3 iron-chelating agents licensed in the UK; desferrioxamine (Desferal®), deferiprone (Ferriprox®) and deferasirox (Exjade®). Desferrioxamine is given as a subcutaneous infusion whereas deferiprone and deferasirox are oral agents. The indications covered by the separate product licenses for each drug differs. A summary of the differing licensed indications is provided in a later section of this bulletin.

Iron chelation is now made easier by the availability of oral iron chelators (especially deferasirox), in addition to parenteral deferoxamine (desferrioxamine). Deferasirox is however frequently associated with gastrointestinal side-effects, and cannot be used in patients with renal failure. Deferiprone, another oral iron chelator, is currently not approved for MDS, and can cause neutropaenia in a small percentage of patients, a side-effect that is problematic in MDS. (2)

A Medicine Information query concerning the clinical and cost effectiveness evidence for the use of iron chelators in the treatment of myelodysplastic syndromes (MDS) was sent to Ipswich Medicine Information department (March 2015).

The information contained within this paper is based upon 3 main references: 1) Cochrane Review: Deferasirox for managing iron overload in people with myelodysplastic syndrome (Review), April 2014., 2) British Committee for Standards in Haematology: Guidelines for the Diagnosis and management of adult myelodysplastic syndromes (Dec 2013), 3) Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up, June 2014,

1) Cochrane Review: Deferasirox for managing iron overload in people with myelodysplastic syndrome (Review), April 2014.

This Cochrane review looked at deferasirox for managing iron overload in people with myelodysplastic syndrome. The following is an extract from this review:

“The benefits of deferasirox have not yet been established in RCTs. Several retrospective analyses and observational studies suggest a benefit with regard to certain outcomes (Excluded studies) (Porter 2004; List 2006, US3 study; Gattermann 2007, EPIC). However, the impact of iron chelation therapy with deferasirox on long-term outcomes or patient-relevant outcomes such as organ dysfunction or mortality has not been established in detail. Since iron chelation therapy had such a positive impact on survival in thalassaemia patients and is now offered to a large group of people, thorough evaluation of iron chelation therapy and deferasirox in particular in people with MDS seems urgently warranted. The generation of further data supporting the application of this intervention instead of no intervention or other iron chelating regimens seems to be even more important considering the costs implied by a continuous therapy with deferasirox (Delea 2005; Karnon 2007; Karnon 2007a; Bozkaya 2008). Also, the profile of adverse effects which might be different for this patient group compared to people with thalassaemia urgently needs to be established to allow adequate balancing of the benefits and potential harms of iron chelation therapy for people with MDS. One prospective randomised trial is currently enrolling patients to answer some of these important questions (TELESTO 2009). This trial should help to define the role of deferasirox and to establish clear indications for iron chelation therapy in MDS patients. The
authors also note that if the effectiveness of deferasirox in MDS is confirmed in the future, further comparisons with other iron chelation regimens such as deferasirox will be worthwhile since e.g. the profile of adverse effects varies between different chelating agents.

2) British Committee for Standards in Haematology: Guidelines for the Diagnosis and management of adult myelodysplastic syndromes (Dec 2013), The British Committee for Standards of Haematology produced their guidelines for the diagnosis and management of adult myelodysplastic syndromes in December 2013. Based on the available evidence, they advised that iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload. However, consideration may be given to its use in other circumstances. Key recommendations are as follows:

Key recommendations from the British Committee for Standards in Haematology Guidelines:
1 Iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload. (Grade 1C)
2 Consideration may be given to chelation therapy for patients with a very good prognosis, specifically patients with WHO RA, RARS and isolated del(5q). Triggers may include more than 20 units of red cells transfused, serum ferritin >1000 ug/l in patients for whom continuing red cell transfusion is predicted. (Grade 2C)
3 Patients treated with iron chelation therapy should ideally receive this treatment within clinical trials.
4 Desferrioxamine remains the therapy of choice with the longest record of safety and efficacy of all three agents available. Deferasirox is recommended for patients intolerant of desferrioxamine. Deferiprone could be considered in patients with normal baseline neutrophil counts. (Grade 2C)

The British Committee Standard in Haematology guidelines also note:
- Deferasirox is the only licensed agent* for iron chelation therapy in MDS (when desferrioxamine therapy is contraindicated or inadequate). The efficacy data used for licensing are phase 2 studies comprising 47 MDS patients out of a total of 1009 (predominantly β thalassaemia) patients (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000670/WC500033929.pdf).
- Larger phase 2 studies have shown a clear reduction in serum ferritin and labile plasma iron species over 1-2 years of therapy but tolerability remains unclear (List, et al 2012). Only half of all patients complete one year of therapy, most due to non-treatment related adverse events. The US Food and Drug Administration (FDA) has added a black box warning to the label for deferasirox for enhanced vigilance with renal impairment, hepatic impairment and gastrointestinal haemorrhage.
- Desferrioxamine remains the therapy of choice as there is the longest duration of clinical experience, it is safe and efficacious if suitably monitored, although somewhat cumbersome compared to its oral competitors. Deferiprone is efficacious but not recommended in neutropenic patients (Cermak, et al 2011).

(*The above wording is taken exactly form the BCSH guidelines. To clarify, deferasirox is the only oral iron chelation therapy licensed)

3) Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in September 2014.
The European Society for Medical Oncology released their guidelines Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in September 2014. They also acknowledge that there is a large debate that exists about the deleterious effect of iron overload in MDS patients and whether iron chelation may be useful in this group of patients with iron overload.
In particular, it is noted in these guidelines that while heart iron overload is a well-documented cause of heart failure in children with thalassaemia, its incidence and clinical consequences are less certain in MDS patients receiving transfusions, particularly as many already have other causes of cardiac morbidity. However, heart MRI studies show that heart iron overload (reflected by a decrease in MRI heart T2*) is frequent in patients having received at least 70–80 RBC concentrates or more, a frequent situation in low-risk MDS and that a heart T2* value <20ms is associated with decreased ventricular ejection fraction and a risk of heart failure. In the absence of prospective studies, published recommendations for iron chelation therapy so far only result from expert opinions, which generally advocate starting chelation in patients with relatively favourable prognosis (i.e. low or intermediate-risk MDS), who have received 20–60 RBC concentrates, or if serum ferritin raises above 1000–2500 U/l, or if cardiac T2* is significantly reduced.

Other information supplied by the Medicines Information department, Ipswich Hospital:
An article published in the Expert Review of Haematology in August 2013 stated the best use of iron chelation therapy (ICT) in myelodysplastic syndrome (MDS) patients with transfusion dependency (TD) and iron overload (IO) is a debated issue. (7) (Increasing evidence highlights the detrimental effects of TD and secondary IO in MDS on the survival and clinical outcomes, including cardiac, hepatic and endocrine damage, and possibly increased infection risk and leukemic transformation. They further state that retrospective data suggest that ICT in MDS with secondary IO can improve survival in some patients with MDS, especially those with lower-risk MDS, may reduce cardiac and hepatic complications, lead to hematologic improvements and possibly decrease leukemic transformation, infectious complications and transplant-related mortality. The traditional use of ICT in MDS has been in patients with lower-risk MDS with TD, but other researchers have argued that the use of ICT in higher-risk MDS patients should be considered to possibly reduce infections, delay leukemic transformation and improve transplantation outcomes. Early prospective data confirm improvements of liver enzymes and hematologic improvements in a significant minority of MDS patients using ICT. The beneficial effects of ICT on organ function and survival in patients with MDS with TD and IO are yet to be demonstrated prospectively in a randomized fashion."

**Licensed indication**

**Desferrioxamine**

Desferrioxamine is licensed for several indications. The relevant indication applicable to MDS is:

Desferrioxamine is licensed for the treatment of chronic iron overload e.g.

- Tranfusional haemosiderosis in patients receiving regular transfusions e.g. thalassaemia major

**Deferasirox**

Deferasirox is licensed for several indications. The relevant indication applicable to MDS is:

For the treatment of iron overload due to blood transfusions when deferoxamine therapy is contra-indicated 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 anaemias aged 2 years and older.

**Deferiprone**
The SPC for deferiprone is more specific, and it is only licensed for:

- The treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.

### Usual dosage

As specified in the respective SPC's

Links attached

Desferrioxamine - [http://www.medicines.org.uk/emc/medicine/2666](http://www.medicines.org.uk/emc/medicine/2666)

Deferasirox - [http://www.medicines.org.uk/emc/medicine/18805](http://www.medicines.org.uk/emc/medicine/18805)

Deferiprone - [http://www.medicines.org.uk/emc/medicine/24631](http://www.medicines.org.uk/emc/medicine/24631)

### Place in therapy

The role of iron chelating therapy in the treatment of iron overload in patients with MDS is an area where clinical trial evidence is lacking and there are unanswered questions. Below is an extract regarding iron chelating therapy from the British Committee for Standards in Haematology: Guidelines for the diagnosis and management of adult myelodysplastic syndromes, British Journal of Haematology, Dec 2013:

**Iron chelation in MDS.**

A chronic red cell transfusion programme for MDS patients results in tissue iron overload. Patients with ineffective erythropoiesis, particularly those with sideroblastic anaemia, often have a baseline excess of body iron. The key questions, yet to be resolved are:

1. **Is tissue iron overload in MDS independently associated with adverse clinical outcome?**

   Transfusion dependence and elevated serum ferritin are independent adverse risk factors for survival in low-risk MDS, particularly in patients with predominantly erythroid disease (WHORA, RARS and del(5q)) (Malcovati et al, 2005). A raised serum ferritin (which may not just reflect iron overload) is an adverse predictor of outcome in myeloablative (MA) stem cell transplantation (Armand et al, 2007).

2. **How best to measure iron loading to reflect the possible adverse clinical outcome?**

   Although serum ferritin is influenced by factors other than iron overload, most guideline recommendations for iron chelation therapy are based upon this parameter. The number of red cell units transfused may be useful but it is likely that transfusion intensity is more relevant for adverse outcome than total units transfused (Malcovati et al, 2006; Durairaj et al, 2011). Magnetic resonance imaging (T2*) can be used to quantitate liver and cardiac iron but the relationship with transfused red cell burden/outcome has not been consistently demonstrated in MDS (Chacko et al, 2007; Di Tucci et al, 2008; Roy et al, 2011).

3. **Can iron chelation therapy influence the natural history of chronically transfused MDS patients?**

   There is no direct evidence to support a survival benefit for iron chelation therapy in MDS and only randomized controlled trials will answer this definitively. A small proportion of patients have improved haematopoiesis on iron chelation. Several studies purporting to demonstrate improved survival for chelated patients are all retrospective and methodologically limited (Rose et al, 2010). Despite this, there is almost universal recommendation in national and international guidelines for iron chelation therapy in selected MDS patients (Greenberg et al, 2011).

4. **Which iron chelation therapy should be used (if any)?**

   Deferasirox is the only licensed agent* for iron chelation therapy in MDS.
when desferrioxamine is contraindicated or inadequate). The efficacy data used for licensing of deferasirox are phase 2 studies comprising 47 MDS patients out of a total of 1009 (predominantly β thalassaemia) patients (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000670/WC500033929.pdf).

Larger phase 2 studies have shown a clear reduction in serum ferritin and labile plasma iron species over 1–2 years of therapy but tolerability remains unclear (List et al, 2012). Only half of all patients complete 1 year of therapy, most due to nontreatment related adverse events. The US Food and Drug Administration (FDA) has added a black box warning to the label for deferasirox for enhanced vigilance with renal impairment, hepatic impairment and gastrointestinal haemorrhage. Desferrioxamine remains the therapy of choice as there is the longest duration of clinical experience, it is safe and efficacious if suitably monitored, although somewhat cumbersome compared to its oral competitors. Deferiprone is efficacious but not recommended in neutropenic patients (Cermak et al 2011).

(*The above wording is taken exactly from the BCSH guidelines. To clarify, deferasirox is the only oral iron chelation therapy licensed)

<table>
<thead>
<tr>
<th>National guidance</th>
<th>NICE : This indication is not covered by NICE guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scottish Medicines Consortium (SMC) (Feb 2007)</td>
<td>Deferasirox (Exjade®) is accepted for restricted use within NHS Scotland for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes. The SMC concluded that &quot;Patients with myelodysplastic syndromes, the commonest cause of transfusion-dependent anaemia, were poorly represented in the clinical trial population and the economic case was not demonstrated in this group.&quot;</td>
</tr>
<tr>
<td>The British Committee Standards in Haematology Guidelines (Dec 2013)</td>
<td>Key recommendations are: 1 Iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload. (Grade 1C) 2 Consideration may be given to chelation therapy for patients with a very good prognosis, specifically patients with WHO RA, RARS and isolated del(5q). Triggers may include more than 20 units of red cells transfused, serum ferritin &gt;1000 lg/l in patients for whom continuing red cell transfusion is predicted. (Grade 2C) 3 Patients treated with iron chelation therapy should ideally receive this treatment within clinical trials. 4 Desferrioxamine remains the therapy of choice with the longest record of safety and efficacy of all three agents available. Deferasirox is recommended for patients intolerant of desferrioxamine. Deferiprone could be considered in patients with normal baseline neutrophil counts. (Grade 2C)</td>
</tr>
</tbody>
</table>

| Local Guidance | There is no local guidance for the use of iron chelating therapy in MDS. Prior to moving to NHSE, the JPC had a negative policy on the use of deferasirox in MDS patients. (Bulletin 115, June 2009). Commissioning responsibility has recently moved back from NHSE to CCGs. |

| Contraindications and Precautions | See individual SPC’s |
| Side effect Profile | |

| Drug Interactions* | See individual SPC’s |
See individual SPC’s

As the drugs are PBR excluded, the exact costs will vary and will be dependent on individual hospitals contracts.

The costs listed below are based on the prices published in the BNF (No.68, Sept 14 – March 2015);

**Desferrioxamine mesilate (generic)**
- 500mg vial £ 4.26, 2g vial £ 17.65

Based on treatment of established iron overload, a typical dose ranges from between 20 – 50mg/kg / day. Treatment is usually given between 3-7 days per week.

**Example of potential cost:**

Based on 70kg patient receiving treatment 7 days week, potential costs can range between £ 4,675 to £ 12,880

NB This figure equates to drug costs only and does not take into account infusion pumps, administration training etc.

**Deferasirox tablets**
- 125mg tablets (28 pack) £ 117.60; 250mg tablets (28 pack) £ 235.20; 500mg tablets (28 pack) £ 470.40

Typical dose ranges from between 10-30mg/kg/day

Potential costs can range between ~£9,200 to £ 24,500.

**Deferiprone tablets**
- 500mg tablets (100 pack) £ 152.39; 1g (50 pack) £ 175.25

NB: Deferiprone is not licensed for use in MDS patients.

**Scottish Medicine Consortium SMC Evaluations (Feb 2007) (9)**

Deferasirox (Exjade®) is accepted for restricted use within NHS Scotland for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes

The SMC state: “Patients with myelodysplastic syndromes, the commonest cause of transfusion-dependent anaemia, were poorly represented in the clinical trial population and the economic case was not demonstrated in this group.”

(April 2013 - The SMC have issued advice stating that the use of deferasirox is not recommended for the treatment of iron overload in patients with non-transfusion dependent thalassaemia syndromes. This decision was derived because the holder of the marketing authorisation had not made a submission to the SMC for this indication.)

A study published in the Journal of Medical Economics in 2010 (Tolley et al) looked at the cost effectiveness of deferasirox compared to desferrioxamine in the treatment of iron overload in lower-risk, transfusion-dependent myelodysplastic syndrome patients. The results from the study suggested that deferasirox is cost effective in lower risk, transfusion-dependent myelodysplastic syndromes patients. The evaluation was based on the results from a cohort of 1000 patients. The incremental cost per QALY gained with deferasirox was £20,822 however this was dependent on the dose of deferasirox used. A dose of 15mg/kg was shown to be less expensive than desferrioxamine whereas a higher dose of 25mg/kg resulted in the incremental
cost per QALY gained rising to over $40,000 (approx. £25,000). This paper was evaluated by the Centre for Reviews and Disseminations (CRD), University of York. The CRD concluded that although the authors of the study concluded that deferasirox was cost effective, the results were based on a key assumption for clinical efficacy. (10) (No clinical trial evidence available hence the phrase key assumption).

The American Journal of Haematology published in May 2011 the article Predicted costs of iron-chelators in myelodysplastic syndromes: A 10-year analysis based on actual prevalence and red cell transfusion rates. They noted that their studies on a cohort of low risk MDS patients indicated the potential increase in costs to health-providers should iron chelation (IC) therapy be adopted as the standard of care in the management of transfusion dependent patients. The finances involved in the delivery and monitoring of IC are likely to add to the drug-costs predicted in this study. Desferrioxamine, for example requires infusion devices for subcutaneous administration or through indwelling venous catheters. In comparison, the increased drug-costs of the orally available chelator Deferasirox may at least partially be offset by its ease of administration with a resulting improvement in quality of life.

Through economic modelling, it has been suggested the use of Deferasirox is likely to be more cost-effective than Desferrioxamine in MDS patients: the cost effectiveness of Deferasirox versus DFO has been estimated to be $31,233–$57,000 (~ £19,000 to £35,000) per quality-adjusted-life years (QALY) gained. However, these economic models are yet to be validated prospectively in clinical studies and to the authors knowledge, there have been few studies on the cost-effectiveness of IC (compared to no chelation as the comparator) in MDS patients. While cost alone should not preclude incorporation of scientific and clinical advances into patient management, a rigorous appraisal of the need, benefits, and cost-utility of novel technologies should be performed prior to recommending changes in clinical practice. (11)

| Potential number of patients in | Based on estimated incidence of 4/100,000 : |
| Bedfordshire and Luton | Bedfordshire CCG (population of 413,484*) |
| Impact per 100,000 population | Potential patient numbers are around 16 patients per year. |
| Affordability considerations | Predicted Annual drug costs: |
|  | If use desferrioxamine: |
|  | Between £75,000 to £206,000 |
|  | (NB This relates to drug cost only and the actual cost will be significantly more as this drug requires to be given via s/C infusion pump therefore will have additional costs) |
|  | If use deferasirox: |
|  | Between £147,000 and £392,000 |
|  | Deferiprone is not licensed for use in MDS patients. |
| Luton CCG (population of 203,641*) | Potential patient numbers are 8 patients per year |
|  | Predicted Annual drug costs: |
|  | If use desferrioxamine: |
|  | Between £38,000 to £103,000 |
(NB This relates to drug cost only and the actual cost will be significantly more as this drug requires to be given via s/C infusion pump therefore will have additional costs)

If use deferasirox:
Between £74,000 and £196,000

Deferiprone is not licensed for use in MDS patients.

It is important to note that the number of patients is likely to be higher as the incidence can increase to around 30/100,000 depending on the age demographic as MDS is predominately a disease affecting people over 70 years. (1) This would significantly increase costs to CCG’s.

*Based on population data from generic NICE costing template

| Evidence strengths and limitations | Awaiting feedback from other EoE CCGs |

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

*Consult Summary of Prescribing Characteristics for full prescribing details.

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

References:

1) British Committee for Standards in Haematology: Guidelines for the Diagnosis and management of adult myelodysplastic syndromes (Dec 2013), British Journal of Haematology, 2014, 164, 503-525


3) Deferasirox for managing iron overload in people with myelodysplastic syndrome (Review), The Cochrane collaboration, Cochrane Library 2014, issue 10


7) Merkel et al. Towards resolving the Unsettled role of iron chelation therapy in myelodysplastic syndromes. Expert Review of Anticancer Therapy, July 2014, vol./is. 14/7(817-829), 1473-7140;1744-8328 (July 2014)

8) Scottish Medicines Consortium - deferasirox, 125, 250, 500mg dispersible tablets (Exjade®) No. (347/07). Jan 2007

9) Cost effectiveness of deferasirox compared to desferrioxamine in the treatment of iron overload in lower-risk, transfusion-dependent myelodysplastic syndrome patients (Structured abstract) Centre for Reviews and Dissemination Original Author(s): Tolley K , Oliver N , Miranda E , Migliaccio-Walle K , Bozkaya D and Li Q Journal of Medical Economics, 2010, 13(3), 559-570

10) Predicted costs of Iron-chelators in myelodysplastic syndromes, a 10 year analysis based on actual prevalence and red cell transfusion rates, American Journal of Haematology, May 2011

11) JPC Bulletin 115 (June 2009): Deferasirox , deferiprone and desferrioxamine
The use of iron chelator therapy for the management of iron overload in patients with myelodysplastic syndromes

JPC Recommendation:

The committee agreed the following recommendation:

- The routine commissioning of iron chelator therapy for the management of iron overload in MDS is not supported.

1) Clinical Effectiveness

- Iron chelation is now made easier by the availability of oral iron chelators (especially deferasirox), in addition to the classical parenteral deferoxamine (desferrioxamine)
- Deferiprone, another oral iron chelator, is currently not approved for MDS and can cause neutropenia in a small percentage of patients, a side-effect that is problematic in MDS.
- The use of iron chelation therapy in the management of iron overload in MDS patients is currently a cause for debate. Clinical trial evidence is lacking and experts acknowledge that there are several unanswered questions around the use of such therapy in this patient group.
- The efficacy data used for licensing of deferasirox was based on phase 2 studies comprising 47 MDS patients out of a total of 1009 (predominantly ß-thalassaemia patients).
- A Cochrane review was undertaken and concluded ‘the benefits of deferasirox have not yet been established in RCTs. Several retrospective analyses and observational studies suggest a benefit with regard to certain outcomes (Excluded studies) (Porter 2004; List 2006, US3 study; Gattermann 2007, EPIC). However, the impact of iron chelation therapy with deferasirox on long-term outcomes or patient-relevant outcomes such as organ dysfunction or mortality has not been established in detail.’
- The Cochrane review reports that there is a randomised trial (TELESTO 2009) underway and that the results of this trial should help define the role of deferasirox and to establish clear indications for iron chelation in MDS.
- The Cochrane review also states that “the profile of adverse effects, which might be different for this patient group compared to people with thalassaemia urgently needs to be established to allow adequate balancing of the benefits and potential harms of iron chelation therapy for people with MDS.
- British Committee Standards in Haematology (BCSH) guidelines (Dec 2013) acknowledge that there is no direct evidence to support a survival benefit for iron chelation therapy in MDS and only randomised controlled trials will answer this definitively.
- Based on the available evidence, the British Committee Standards in Haematology (BCSH) Guidelines advise that iron chelation therapy cannot be routinely recommended for MDS patients with transfusional iron overload. However, consideration may be given to its use in certain circumstances. (NB: The BCSH guidelines also acknowledge that there is almost universal recommendation in national and international guidelines for iron chelation therapy in selected MDS patients (Greenberg et al 2011).)
- If treatment is to be used, the BCSH guidelines state that desferrioxamine remains the therapy of choice with the longest record of safety and efficacy of all three agents available. Deferasirox is recommended for patients intolerant of desferrioxamine. Deferiprone could be considered in patients with normal baseline neutrophil counts.
- BCSH guidelines also state that patients treated with iron chelation therapy should ideally receive this treatment within clinical trials.
An article published in Expert Review of Haematology (2013) states that retrospective data suggests that iron chelation therapy can improve survival in MDS, especially lower risk MDS, may reduce cardiac and hepatic complications, lead to haematologic improvements and possibly decrease leukaemic transformation, infectious complications and transplant related mortality. The authors also state that the beneficial effects of iron chelation therapy on organ function and survival in MDS have yet to be demonstrated prospectively in a randomised fashion.

- The US food and Drug Administration (FDA) has added a black box warning for deferasirox for enhanced vigilance with renal impairment, hepatic impairment and gastrointestinal haemorrhage.

### 2) Cost Effectiveness

**Scottish Medicines Consortium (2007)**

Deferasirox (Exjade®) is accepted for restricted use within NHS Scotland for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes.

The SMC state: "Patients with myelodysplastic syndromes, the commonest cause of transfusion-dependent anaemia, were poorly represented in the clinical trial population and the economic case was not demonstrated in this group."

(April 2013 - The SMC have issued advice stating that the use of deferasirox is not recommended for the treatment of iron overload in patients with non-transfusion dependent thalassaemia syndromes. This decision was derived because the holder of the marketing authorisation had not made a submission to the SMC for this indication.)

A study published in the Journal of Medical Economics in 2010 (Tolley et al) looked at the cost effectiveness of deferasirox compared to desferrioxamine in the treatment of iron overload in lower-risk, transfusion-dependent myelodysplastic syndrome patients. The results from the study suggested that deferasirox is cost effective in lower risk, transfusion-dependent myelodysplastic syndromes patients. This paper was evaluated by the Centre for Reviews and Disseminations (CRD), University of York. The CRD concluded that although the authors of the study concluded that deferasirox was cost effective, the results were based on a key assumption for clinical efficacy.

A further economic study was published in The American Journal of Haematology published in May 2011: Predicted costs of iron-chelators in myelodysplastic syndromes: A 10-year analysis based on actual prevalence and red cell transfusion rates. The authors acknowledge that economic models are yet to be validated prospectively in clinical studies and to their knowledge, there have been few studies on the cost-effectiveness of IC (compared to no chelation as the comparator) in MDS patients.

**The following costs are an estimation of the cost of treatment:**

Based on estimated incidence of 4/100,000:

**Bedfordshire CCG (population of 413,484*)**

Potential patient numbers are around 16 patients per year.

**Predicted Annual drug costs:**

**If use desferrioxamine:**

Between £80,000 to £210,000

(NB This relates to drug cost only and the actual cost will be significantly as this treatment requires infusion pumps, training etc)

**If use deferasirox:**
Between £129,000 and £392,000

Deferiprone is not licensed for use in MDS patients.

Luton CCG (population of 203,641*)
Potential patient numbers are 8 patients per year

Predicted Annual drug costs:

If use desferrioxamine:
Between £40,000 to £105,000
(NB This relates to drug cost only and the actual cost will be significantly more as this drug requires to be given via s/C infusion pump therefore will have additional costs)

If use deferasirox:
Between £64,000 and £196,000

Deferiprone is not licensed for use in MDS patients.

It is important to note that the number of patients is likely to be higher as the incidence can increase to around 30 / 100,000 depending on the age demographic as MDS is predominately a disease affecting people over 70 years (1). This would significantly increase cost.

*Based on population data from generic NICE costing template

3) Equity
None identified

4) Needs of the community
Based on estimated incidence of 4/100,000:

Bedfordshire CCG (population of 413,484*)
Potential patient numbers are around 16 patients per year.

Luton CCG (population of 203,641*)
Potential patient numbers are 8 patients per year

It is important to note that the number of patients is likely to be higher as the incidence can increase to around 30 / 100,000 depending on the age demographic as MDS is predominately a disease affecting people over 70 years (1). This would significantly increase cost.

*Based on population data from generic NICE costing template

5) Need for healthcare (incorporates patient choice and exceptional need)
There is no alternative treatment. Consequences of not treating awaiting confirmation from Haematology specialists

6) Policy drivers
SMC/British Committee Standards in Haematology Guidelines

7) Disinvestment
The JPC agreed the following sections within the CCG Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

N:\Medicines Management\JPC\Agenda and minutes\April 15\Papers for circulation\5.3 The use of iron chelators in MDS.docx
### Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 1*)</th>
<th>Step 2 (Level 2*)</th>
<th>Step 3 (Level 3*)</th>
<th>Step 4 (Level 4*)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Local and current random sample surveys (or census)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Systematic review of inception cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Inception cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Randomized trial or observational study with dramatic effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>What are the common harms? (Treatment Harms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>What are the rare harms? (Treatment Harms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Systematic review of randomized trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Randomized trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".


* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thompson, Olive Goddard and Mary Hodgkinson