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<td>Lead Executive/Director:</td>
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<td>Mandy Matthews</td>
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<td>Target audience:</td>
<td>NHS Worcestershire GP practices All providers</td>
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<td>6th April 2011</td>
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<tr>
<td>Policy amendment approved by Worcestershire Area Prescribing Committee</td>
<td>6th April 2011</td>
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Deferasirox in the treatment of transfusional iron overload in thalassaemia major and other anaemias.

CONTRIBUTION LIST

Key individuals involved in developing the document

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<tr>
<th>Name</th>
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Circulated to the following individuals for comments

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<td>APC members</td>
<td>Area Prescribing Committee</td>
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Approval Committees:

Worcestershire Area Prescribing Committee (APC) has recommended approval of this policy on 7th December 2010.
NHS Worcestershire Commissioning Executive ratified this policy on 20th December.

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1.0 Recommendation:

Following an assessment of the evidence for use of deferasirox for the treatment of transfusional iron overload in patients with thalassaemia major and other anaemias, the Area Prescribing Committee recommends the following:

- Deferasirox, within its marketing authorisation, may be considered as an option in treating transfusional iron overload in children with thalassaemia major or other anaemias.
- Desferrioxamine should remain first line treatment of transfusional iron overload in adults. In all groups, deferasirox should be considered as second line therapy only in adult patients unable to tolerate desferrioxamine or those experiencing severe adverse effects. It should not be used as a treatment option solely due to patient preference.
- In patients with myelodysplastic syndrome who are intolerant, experience severe adverse effects or are unresponsive to desferrioxamine, and would otherwise have continued on a suboptimal dose of desferrioxamine, the use of deferasirox should be further restricted to transfusion dependent patients with low-risk (IPSS low or Int-1) myelodysplastic syndrome for whom the predicted survival is greater than 4 years. It should not be used as a treatment option solely due to patient preference.

2.0 Definitions:

2.1 Treatment means any form of healthcare intervention which has been proposed by a clinician and is proposed to be administered as part of NHS commissioned and funded healthcare.

2.2 An individual funding request is a request received from a provider, or a patient with explicit support from a clinician, which seeks funding for a single identified patient for a specific treatment.

2.3 Exceptional clinical circumstances refers to a patient who has clinical circumstances which, taken as a whole, are outside the range of clinical circumstances presented by a patient within the normal population of patients with the same medical condition and at the same stage of progression as the patient.

2.4 Responsible Primary Care Trust means the Primary Care Trust which discharges the Secretary of State’s functions under the National Health Service Act 2006 for an individual patient.

3.0 Purpose:

3.1 This policy has been developed to support cost-effective prescribing of medicines within NHS Worcestershire.

3.2 This policy applies to any patient for whom NHS Worcestershire is the Responsible Commissioner.

3.3 NHS Worcestershire is prepared to consider providing funding outside of the above recommendations for individual patients who are able to demonstrate exceptional clinical circumstances. Any such applications will be considered by the PCT under its Individual Funding Request policy and other relevant policies and operating procedures.

3.4 The purpose of this policy is to ensure diversity and equality to all patients, irrespective of their gender, race, ethnic origin, disability,
age, nationality, national origin, sexuality, religion or belief, marital status and social class. We oppose all forms of unlawful and unfair discrimination.

4.0 Background:

4.1 Iron overload is the main complication of regular blood transfusions which are used in the management of several conditions including the beta thalassaemias (β-TM), sickle cell disease (SCD), myelodysplastic syndrome (MDS) and other rare anaemias.

4.2 Complications of untreated iron overload include iron related cardiomyopathy, lung defects, liver cirrhosis, pituitary damage and reduced life expectancy.

4.3 There are three drugs licensed within the UK for the treatment of iron overload.

4.4 Desferrioxamine (Desferal®) (DFO) is delivered by a subcutaneous infusion over 8-12 hours, 5 to 7 times per week usually within the home. It is licensed within the UK for treatment of iron overload in patients suffering from β-TM, SCD and MDS, as well as other transfusion-dependent anaemias and iron-loading conditions. The recommended dose is 20-50mg/kg/day. The annual drug cost for a 70kg person receiving 5 transfusions per week ranges from £3,322.80-£7,755.80 for doses of 20-50mg/kg respectively although costs of infusional equipment also impact on overall treatment costs.

4.5 Deferiprone (Ferriprox®) (DFP) is a three times daily oral dose treatment which is licensed for thalassaemia patients over the age of 6 years in whom DFO is contraindicated or is not tolerated. Recommended dose is 75-100mg/kg/day. The annual drug cost for a 70kg person ranges from £6117.40-£7,785.45 for doses of 75-100mg/kg respectively.

4.6 Deferasirox (Exjade®) (DFX) is a single daily dose oral treatment supplied as a dispersible tablet which is licensed for the treatment of chronic iron overload in adults and children over 6 years with thalassaemia major who receive frequent blood transfusions. It is also licensed when DFO is contra-indicated or inadequate in those with infrequent transfusions, in patients with other anaemias, and in children aged 2 to 5 years. The recommended dose is 20-50mg/kg/day. The annual drug cost for a 70kg person ranges from £9,198-£26,061 for doses of 20-50mg/kg respectively.

4.7 There are three separate randomised controlled trials of clinical efficacy of DFX in comparison to DFO. Two trials included patients with thalassaemia1,2 and one included patients with SCD3. Overall DFX (20mg/kg) appears comparable to DFO (40mg/kg) in reduction of liver iron concentration levels. Given the relative short time frame of all DFX clinical efficacy studies, relationship to longer term morbidity and mortality has not been established. No trials compare DFX to DFP treatment.

4.8 With regard to patients with other anaemias, there are no RCTs and no cohort studies comparing DFX with other iron chelation therapies. Observational studies suggest that DFX has a significant
effect on indices of iron overload in patients with anaemias other than due to thalassaemia or sickle cell disease, but they do not establish DFX as non-inferior to existing treatments.

4.9 Within a research setting, DFX has a safety profile which is comparable to DFO although in further monitoring outside of research trials, concerns have been raised regarding renal and hepatic impairment, and gastrointestinal haemorrhage which have led to safety alerts.

4.10 Five published studies have examined cost-effectiveness of DFX in comparison to other iron overload treatments. Overall the economic analyses suggest that DFX is cost-effective in patients with β-TM, SCD and MDS, with stronger evidence of cost-effectiveness in younger and lighter patients. DFX treatment dominates (is cheaper) for average weight SCD (42kg) and beta-thalassaemia patients (52kg) and costs are estimated at £7,775 per QALY for those weighing 62kg and £16,720 per QALY for those 72kg, all on 20mg/kg DFX v. 35mg/kg DFO. In MDS patients, the cost of DFX compared to DFO treatment within an NHS setting has been estimated at £20,822 per QALY for a patient weighing 70kg on 20mg/kg DFX v 40mg/kg DFO.

5.0 Evidence:

5.1 In a large (n=586) Phase III RCT of patients with β-TM, it was found that doses of DFX 10mg/kg/d given to those with liver iron concentrations (LIC) less than 7mg Fe/g dry weight (dw) were inferior to DFO treatment with only 40% of DFX treated participants reducing LIC levels compared to 83% of those treated with DFO. For those with baseline LIC levels ≥ 7mg Fe/g/dw, similar numbers in each treatment arm (DFX 58.6% mean dose 25mg/kg v DFO 58.9% mean dose 47mg/kg) showed reductions in LIC after a year. Some concerns with measurement accuracy of LIC make interpretation of the results of this trial complex however in those receiving the higher doses of DFX, treatment effects appear similar to doses of DFO after 1 year. Mild and generally transient adverse effects were reported with increased serum creatinine in 38%, gastrointestinal events in 15.2% and skin rashes in 10.8% of those treated with DFX. Adverse effects resulted in discontinuation in 5.7% v. 4.1% of participants in DFX and DFO groups respectively.

5.2 A Phase II RCT (n=71) of participants with β-TM with doses of 10mg/kg DFX found not to be effective in reducing iron overload but similar effects in terms of reduction of LIC in those treated with 20mg/kg DFX and 40mg/kg DFO. Almost all participants reported some form of adverse event (97.9% DFX; 91.3% DFO) although these were again generally mild and only resulted in one discontinuation.

5.3 A Phase II RCT in patients with SCD (n=203) also found significant reductions in LIC in both treatment groups over a 48 week follow-up. Although statistical comparison of these reductions was not reported, they were noted as being "similar" in the text. Similar rates of serious adverse events were noted in patients, 46.2% and 42.9%
for DFX and DFO respectively. Raised serum creatinine was seen in 36.4% of patients on DFX compared to 22.2% of those on DFO.

5.4 The large observational EPIC study⁴ (n=1744) included 341 patients with MDS, 116 with aplastic anaemia, 43 with rare anaemias and 49 with other transfused anaemias who were treated for one year with DFX. Initial dose of DFX was set according to transfusion history and adjusted according to treatment response. Significant reductions in serum ferritin were noted (-264 ng/mL, p<0.0001), with no statistically significant differences across disease groups.

5.5 An HTA review⁵ concluded that DFX performs as well as DFO in reduction of iron liver concentrations for patients with thalassaemia or SCD.

5.6 A US study provided an economic evaluation of use of DFX in patients with β-thalassaemia.⁶ The study used a life time (50 year) time frame and assessed direct costs within the US medical system of drugs, administration and treatment of cardiac disease. Treatment with DFX versus DFO was compared and based on an Australian study, treatment with DFX was assumed to provide a utility of 0.85 compared to 0.61 for infused DFO treatment. Compliance was estimated to be 74% with DFX versus 64% with DFO and to impact on risk of development of cardiac disease. Adverse events of treatment were not considered. Overall treatment with DFX results in an increase of 4.5 QALYs at a cost of $126 018, ICER $28 255 per QALY. Sensitivity analyses reported in the Delea paper suggest that cost-effectiveness is more favourable in younger children $28255 per QALY for those starting at 3 years and $76 459 per QALY at 40 years, reflecting shorter life expectancy and increasing drug costs with increasing patient weight.

5.7 Karnon et al (2008)⁷ used a UK perspective over a one year time frame and also monitored direct costs of drugs, administration and treatment of adverse drug effects. Costs were as at 2007 and compliance was assumed to be equal. DFX was found to be less expensive and more effective than DFO in the reference thalassaemia patient, estimated to be 42kg and sickle cell patient estimated to be 52kg. For a patient weighing 62kg, cost per QALY was £7775 and at 72kg, £16,720 for DFX treatment against DFO. The results suggest that for thalassaemia and sickle cell disease, DFX treatment is likely to be cost-effective compared to DFO but extension to other conditions is uncertain.

5.8 As part of the HTA review⁵ a cost-effectiveness analysis was conducted of DFX in comparison to DFO and DFP for patients with β-thalassaemia and sickle cell disease. Given the lack of long-term data on effectiveness of DFX treatment, a one-year model was used. Costs of drugs and administration were considered although costs of adverse events were not. Costs of mode of administration of DFO by balloon infuser or traditional pump were also considered. Patient weights were estimated with reference to weight data for a range of SCD patients from 0-18 years. Compared to DFO administered by traditional pump, DFX is cost-effective to
approximately 6 years of age (ICER < £20,000 per QALY), over age 10 it is unlikely to be cost-effective (ICER >£30,000). If DFO is administered by the more expensive balloon infuser, treatment with DFX is the dominant therapy (cheaper and more effective) to approximately 14 years. Above age 14, DFO is cost-effective. In comparison to DFP, and assuming both treatments provide the same utility (valued equally by patients), DFX is not cost-effective at any age. The HTA review concludes that DFX is generally cost-effective compared to DFO, dependent on mode of administration of DFO, but is not cost-effective compared to DFP. It is noted that this analysis does not consider cost of adverse events due to treatment. DFP has been shown to be associated with some costly adverse events such as agranulocytosis and thus this approach may bias towards a finding of cost-effectiveness of DFP.

5.9 A South Korean study\(^8\) compared DFO administered in hospital (the only option in South Korea), compared to DFX treatment at home. A 50 year time-frame was taken with patients assumed to start therapy at 50 years of age and to weigh 50kg. Compliance with DFX was estimated at 74% and with DFO at 64%. A wider societal perspective was taken so patient costs associated with hospital based treatment were also included. In the cost-utility analysis, DFX was the dominant therapy until differences in compliance exceeded 14% although it remained cost-effective within reasonable variations in compliance.

5.10 Most recently, Tolley et al (2010)\(^9\) have modelled costs of DFX treatment in comparison to treatment with DFO for low risk patients with MDS. An NHS perspective was taken and future costs and outcomes were discounted 3.5%. In the reference case of a 70kg patient with a dose of 20mg/kg DFX or 40mg/kg DFO on 5 days per week, there was an incremental cost per QALY of £20,822 for treatment with DFX compared to treatment with DFO. Sensitivity analyses demonstrated that with a higher patient weight or a higher dose of DFX, treatment would be less cost-effective, e.g. cost per QALY in an 80kg patient (£29,509) or one on a dose of 25mg/kg (£42,109).

5.11 Deferasirox (Exjade ®\(^\text{\textregistered}\)\(^\text{\textbullet}\) appears on the Black Triangle list of the Medicines and Healthcare products Regulatory Agency (MHRA).

5.12 Deferasirox is approved for treatment of chronic iron overload due to frequent blood transfusions in patients with beta-thalassaemia major aged 6 years and older and in patients with other anaemias, those aged 2-5 years and overload due to infrequent blood transfusions where DFO is contraindicated or inadequate by the All Wales Medicines Strategy Group (June 2008).

5.13 In NHS Scotland Deferasirox is approved for treatment of chronic overload associated with inherited anaemias. It is not recommended for those with MDS due to lack of clinical trial data and lack of an economic case (January 2007).

5.14 Pan Birmingham Cancer Network approves use of DFX in low risk (IPSS low or Int-1) MDS patients aged under 70 years. Usual first line therapy is noted as DFO (May 2010).
5.15 An evaluation of the use of iron chelation therapy is due to be considered by the National Institute of Health and Clinical Excellence (NICE); this guidance will be reviewed in light of any recommendations made by NICE.

6.0 Documents used to inform this document:


6.3 Guidelines for the Management of Adult Myelodysplastic Syndromes, Pan Birmingham Cancer Network, May 2010

7.0 References:


8.0 Equality Impact Assessment Report Template

8.1 Name of policy or function: Deferasirox in the treatment of transfusional iron overload in thalassaemia major and other anaemias

8.2 Responsible Manager: Mandy Matthews, New Drugs & Technologies Manager

8.3 Date EIA completed: 13th April 2011

8.4 Description of aims of function/policy:
   8.4.1 To support cost effective prescribing of medicines in NHS Worcestershire.
   8.4.2 To ensure appropriate use of NHS resource
   8.4.3 To strengthen the process of Medicines Management to make the best of use of resources.

8.5 Brief summary of research and relevant data: Not Applicable

8.6 Methods and outcomes of consultation: Not Applicable

8.7 Results of Initial Screening or Full Equality Impact Assessment

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8.8 Decisions and or recommendations (including supporting rationale): Not Applicable

8.9 Equality action plan (if required): Not Applicable

8.10 Monitoring and review arrangements (include date of next full review):

   The policy will be reviewed in two years, or sooner if any recommendations are made by the National Institute for Health and Clinical Excellence (NICE).

   The effectiveness of the policy will be reviewed against:
   • Secondary Care Providers contract monitoring (normally monthly)
   • Complaints Process
   • Individual Funding Requests for treatment