Ferumoxytol (Feraheme) for iron deficiency anaemia not associated with chronic kidney disease – first or second line

SUMMARY

Ferumoxytol is intended as an additional or alternative parenteral iron therapy for the treatment of episodic iron deficiency anaemia (IDA) in adult patients when oral iron preparations are contraindicated, not tolerated or ineffective. If licensed, ferumoxytol would provide an additional option for parenteral iron treatment. It can be delivered over short infusions and requires a total of only 1 to 2 doses. Ferumoxytol is an iron oxide semi-synthetic nanoparticle with a polyglucose sorbitol carboxymethyl ether coating formulated with mannitol. This product is a new formulation for iron replacement therapy that aims to achieve high-dose repletion in a single administration without the requirement for a test dose. Ferumoxytol is already licensed in the USA and in pre-registration in the EU for the treatment of IDA in adult patients with CKD.

Iron deficiency anaemia is the most common cause of anaemia worldwide, causing between 15 to 36% of all cases. In the developed world, 2-5% of adult men and postmenopausal women, and 5–12% of otherwise healthy pre-menopausal women have IDA. The WHO defines anaemia as a haemoglobin level below 13g/dL in men over 15 years, below 12g/dL in non-pregnant women over 15 years, and below 11g/dL in pregnant women. Haemoglobin values below 8g/dL have been associated with impaired physical work capacity, reproductive efficiency, and cognitive and psychomotor development. Low maternal haemoglobin concentrations can be markers for increased risk of low birth weight and perinatal mortality.

Current options for the treatment of IDA include oral iron therapy (i.e. ferrous sulphate, ferrous fumarate and ferrous gluconate), ascorbic acid (which may enhance iron absorption), parenteral iron (i.e. iron sucrose, ferric carboxymaltose, iron (III) hydroxide dextran and iron isomaltoside) and blood transfusions. Ferumoxytol is currently in phase III clinical trials comparing its effect on blood haemoglobin concentrations against placebo or iron sucrose.
TARGET GROUP

- Iron deficiency anaemia (IDA): not associated with chronic kidney disease (CKD) first or second line.

TECHNOLOGY

DESCRIPTION

Ferumoxytol (Feraheme, Rienso, ferrosferric oxide) is an iron oxide semi-synthetic nanoparticle with a polyglucose sorbitol carboxymethylether coating formulated with mannitol. This product is a new formulation for iron replacement therapy that aims to achieve high-dose repletion in a single administration without the requirement for a test dose\(^1\). Ferumoxytol allows up to 510mg of iron to be administered in a single dose in patients with CKD\(^1\). Ferumoxytol is intended as an additional or alternative therapy for the treatment of episodic iron deficiency anaemia (IDA) in adult patients when oral iron preparations are contraindicated, not tolerated or ineffective. Ferumoxytol is administered by intravenous (IV) injection at 510mg on day 1, with a second dose of 510mg given 2 to 8 days later.

Ferumoxytol is already licensed in the USA and pre-registration in the EU for the treatment of IDA in adult patients with CKD. During clinical trials serious hypersensitivity reactions were reported in 0.2% of subjects. Other common adverse events include; nausea, dizziness, hypotension, headache, oedema, vomiting, abdominal pain, chest pain, cough, pruritus, pyrexia, back pain, muscle spasms, dyspnoea and rash (<5%)\(^2\).

Ferumoxytol is in phase II clinical trials as an imaging agent in magnetic resonance imaging, and phase III clinical trials for IDA in CKD patients.

INNOVATION and/or ADVANTAGES

If licensed, ferumoxytol would provide an additional option for patients requiring parenteral iron therapy. Ferumoxytol can be delivered over short infusions and requires a total of only 1 to 2 doses.

DEVELOPER

Takeda Ltd.

PATIENT GROUP

BACKGROUND

The WHO defines anaemia as a haemoglobin (Hb) level below 13g/dL in men over 15 years, below 12g/dL in non-pregnant women over 15 years, and below 11g/dL in pregnant women\(^3\). The commonest cause of IDA in pre-menopausal women is menstrual blood loss, followed by increased demands in pregnancy, breast-feeding and dietary deficiency\(^3\). Other causes of IDA include GI tract malignancies, other GI disorders, postpartum haemorrhage, malabsorption (most frequently from coeliac disease in the UK), poor dietary intake, blood
donation, gastrectomy and the use of non-steroidal anti-inflammatory drugs\textsuperscript{3,4}. Asymptomatic colonic and gastric carcinoma may present with IDA and seeking these conditions is a priority in managing patients with IDA.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:
- Equity and Excellence: Liberating the NHS (2010).

**CLINICAL NEED and BURDEN OF DISEASE**

IDA is the most common cause of anaemia worldwide, causing between 15 to 36\% of all cases\textsuperscript{5}. In the developed world, 2-5\% of adult men and postmenopausal women, and 5–12\% of otherwise healthy pre-menopausal women have IDA\textsuperscript{3}. Blood loss from the gastrointestinal (GI) tract is the commonest cause of IDA in adult men and post-menopausal women, accounting for 4-13\% of referrals to gastroenterologists\textsuperscript{3}. In England there were 66,166 admissions for IDA (ICD10 D50), resulting in 77,112 bed days and 77,559 finished consultant episodes in 2010-11\textsuperscript{6}. Only a small proportion of those receiving oral iron therapy will be refractory to treatment and require parenteral iron\textsuperscript{a}. These patients are most commonly those with Crohn’s disease, bowel surgery, bariatric surgery, and women with menorrhagia\textsuperscript{a}. Patients with cardiac failure whose cardiac function could benefit from iron supplementation and perioperative patients undergoing an enhanced recovery programme (e.g. patients with colon cancer) may also be referred for parenteral iron\textsuperscript{a}. In England and Wales, 7,193,299 items for oral iron supplementation and 2,961 items for parenteral iron supplementation were dispensed in the community in 2011, at a cost of £14,118,409 and £104,081, respectively\textsuperscript{7,8}. In one NHS Hospital Trust serving a population of 60,000 people, 124 people received parenteral iron in 2010-11\textsuperscript{a}; if that level of need was replicated across England and Wales, around 114,000 people might require treatment with parenteral iron each year.

Hb values below 8g/dL have been associated with impaired physical work capacity, reproductive efficiency, and cognitive and psychomotor development\textsuperscript{5}. Hb values below 8g/dL have been associated with impaired physical work capacity, reproductive efficiency, and cognitive and psychomotor development\textsuperscript{5}. Epidemiological studies suggest that maternal Hb concentrations at either the low or high end of the distribution during pregnancy (usually in the first or second trimester) are markers of increased risks of low birth weight and perinatal mortality\textsuperscript{5}. Iron deficiency may contribute to maternal morbidity through increased susceptibility or severity of infections, poor work capacity and performance, and disturbances of postpartum cognition and emotions\textsuperscript{10}.

\textsuperscript{a} Expert communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia. 2008\(^{11}\).
- NICE clinical guideline. Multiple pregnancy: the management of twin and triplet pregnancies in the antenatal period. 2011\(^{12}\).
- NICE clinical guideline. Coeliac disease: Recognition and assessment of coeliac disease. 2009\(^{13}\).
- NICE clinical guideline. Antenatal care: Routine care for the healthy pregnant woman. 2008\(^{14}\).
- NICE clinical guideline. Heavy menstrual bleeding. 2007\(^{15}\).
- NICE clinical guideline. Nutrition support in adults: Oral nutrition support, enteral tube feeding and parenteral nutrition. 2006\(^{16}\).
- NICE clinical guideline. Referral for suspected cancer. 2005 (updated 2011)\(^{17}\).
- NICE clinical guideline. Dyspepsia: Managing dyspepsia in adults in primary care. 2004\(^{18}\).
- NICE interventional procedure guidance. Wireless capsule endoscopy for investigation of the small bowel: guidance. 2004\(^{19}\).

Other Guidance

- British Committee for Standards in Haematology. UK guidelines on the management of iron deficiency in pregnancy. 2011\(^{20}\).
- British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. 2011\(^{3}\).
- Scientific Advisory Committee on Nutrition. Iron and Health. 2011\(^{9}\).
- Royal College of Obstetricians and Gynaecologists. Postpartum haemorrhage, Prevention and Management. 2009\(^{20}\).
- Royal College of Obstetricians and Gynaecologists. Blood Transfusions in Obstetrics. 2007\(^{21}\).
- Department of Health. Better Blood Transfusion. 2007\(^{22}\).
- WHO. Iron deficiency anaemia: assessment, prevention and control. 2001\(^{23}\).

EXISTING COMPARATORS and TREATMENTS

Current options for the treatment of IDA include\(^{3,24}\):

- Oral therapy
  - ferrous sulphate
  - ferrous fumarate
  - ferrous gluconate
  - ascorbic acid (may enhance iron absorption)
- Parenteral iron – for those intolerant to, or not responding to oral iron.
  - iron sucrose (Venofer)
  - ferric carboxymaltose (Ferinject)
  - iron (III) hydroxide dextran (Cosmofer)
• iron isomaltoside (Monofer)

Blood transfusions – for the elderly, those with symptomatic anaemia despite iron therapy, or those at risk of cardiovascular instability because of the degree of their anaemia.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01114139, AMAG-FER-IDa-301; ferumoxytol or placebo; phase III.</th>
<th>NCT01114217, AMAG-FER-IDa-303; ferumoxytol single arm; phase III extension.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>AMAG Pharmaceuticals, Inc.</td>
<td>AMAG Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry[^25,26^], manufacturer.</td>
<td>Trial registry[^27,28^], manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA and India.</td>
<td>USA, Canada and India.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=800 (planned); adults; IDA; inadequate response or intolerance/ contraindications to oral iron therapy.</td>
<td>n=600 (planned); adults; IDA; completed trial NCT01114139.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to ferumoxytol 510mg on day 1 with a second dose given 2 to 8 days later, or placebo. All administered IV.</td>
<td>Active treatment group and placebo group from previous trial both received ferumoxytol 510mg on day 1 with a second dose given 2 to 8 days later. Whether placebo group from trial NCT01114139 crossed over to active treatment is not reported.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 6 months.</td>
<td>Active treatment period 6 months.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Change in Hb.</td>
<td>Change in Hb.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Change in vitality score from 36-item Short-Form General Health Survey (SF-36), change in energy scale from the Quality of Life (QoL) Linear Analog Scale Assessment (LASA).</td>
<td>Change in vitality score from SF-36, change in energy scale from QoL LASA.</td>
</tr>
</tbody>
</table>

[^25]: Sponsor AMAG Pharmaceuticals, Inc.
[^26]: Source of information Trial registry[^25,26^], manufacturer.
[^27]: Sponsor Auerbach Hematology Oncology Associates P C.
[^28]: Source of information Trial registry[^27,28^], manufacturer.
[^29]: Sponsored by Auerbach Hematology Oncology Associates P C.
[^30]: Sponsored by Auerbach Hematology Oncology Associates P C.

[^b]: Expert communication.
Participants

<table>
<thead>
<tr>
<th>Participants</th>
<th>n=600 (planned); adults; IDA; inadequate response or intolerance/ contraindications to oral iron therapy.</th>
<th>n=60 (planned); adults; IDA; Hb levels of &lt;11.0g/dL; inadequate response or intolerance/contraindications to oral iron therapy.</th>
</tr>
</thead>
</table>

Schedule

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Randomised to ferumoxytol 510mg on day 1 with a second dose given 2 to 8 days later, or iron sucrose 1g administered in 5 x 200mg doses.</th>
<th>Ferumoxytol 1.020mg IV administered over 15 minutes.</th>
</tr>
</thead>
</table>

Follow-up

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>5 weeks.</th>
<th>5 weeks.</th>
</tr>
</thead>
</table>

Primary outcome/s

<table>
<thead>
<tr>
<th>Primary outcome/s</th>
<th>Change in Hb.</th>
<th>Efficacy (definition and measurements used are not reported).</th>
</tr>
</thead>
</table>

Secondary outcome/s

<table>
<thead>
<tr>
<th>Secondary outcome/s</th>
<th>Change in vitality score from SF-36, change in energy scale from QoL LASA.</th>
<th>Safety.</th>
</tr>
</thead>
</table>

Expected reporting date

<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>Not reported.</th>
<th>Not reported.</th>
</tr>
</thead>
</table>

ESTIMATED COST and IMPACT

COST

The cost of ferumoxytol is not yet known. The costs for other selected treatments are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Weekly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran (Cosmofer)</td>
<td>200mg IV or IM, up to three times weekly.</td>
<td>£48</td>
</tr>
<tr>
<td>Iron sucrose (Venofer)</td>
<td>200mg IV, up to three times weekly.</td>
<td>£56</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Ferinject)</td>
<td>≤15mg/kg (maximum dose 1,000mg) IV, once weekly.</td>
<td>£191</td>
</tr>
<tr>
<td>Iron isomaltoside (Monofer)</td>
<td>100-200mg IV, up to three times weekly.</td>
<td>£51-£102</td>
</tr>
</tbody>
</table>

IMPACT - SPECULATIVE

Impact on Patients and Carers

☐ Reduced mortality/increased length of survival ☐ Reduced symptoms or disability
☐ Other:
  Specify, e.g. improved patient convenience ☐ No impact identified

Impact on Services

☐ Increased use of existing services ☐ Decreased use of existing services
☐ Re-organisation of existing services ☐ Need for new services
☐ Other ☐ None identified

c Based on average adult bodyweight 76.9kg.
Impact on Costs

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES

26 Clinical Trials Registry – India (CRI). A clinical trial to study the safety and efficacy of ferumoxytol for the treatment of iron deficiency anemia.
28 Clinical Trials Registry – India (CRI). A clinical trial to study the safety and efficacy of ferumoxytol for the episodic treatment of Iron Deficiency Anemia.