Epoetin alfa (Eprex) for anaemia in adults with low or intermediate-1 risk myelodysplastic syndromes

LAY SUMMARY

Myelodysplastic syndromes are a group of rare diseases which affect the bone marrow – the part of the body where blood cells are made. In myelodysplastic syndromes, the bone marrow does not make enough healthy blood cells. This causes symptoms such as feeling weak, tired and breathless due to lack of red blood cells (anaemia).

Epoetin alfa is a drug not currently licensed but already used for the treatment of anaemia in adults with myelodysplastic syndromes that is injected under the skin. If epoetin alfa is licensed for use in the UK, it would be the first drug specifically for these patients, and could improve their quality of life.

NIHR HSRIC ID: 12118
TARGET GROUP

- Anaemia in adults with myelodysplastic syndromes (MDS): haemoglobin level <10g/dL; International Prognostic Scoring System low or intermediate-1 risk.

TECHNOLOGY

DESCRIPTION

Epoetin alfa (Eprex; epoetin-α; recombinant human EPO) is a recombinant form of human erythropoietin. The recombinant protein has the same mechanism of action as endogenous human erythropoietin, a protein produced by the kidneys to stimulate the production of red blood cells in the bone marrow. In the phase III clinical trial, epoetin alfa was presented in a pre-filled syringe and administered subcutaneously (SC) at 337.5 to 1,050IU/kg once weekly1.

Epoetin alfa (as Eprex) is licensed in the EU for the treatment of symptomatic anaemia associated with chronic renal failure and anaemia in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma. It is also indicated for use in adults in a pre-donation programme to increase the yield of autologous blood and for non-iron deficient adults prior to major elective orthopaedic surgery. Very common and common (≥1%) reported adverse events include diarrhoea, nausea, vomiting, pyrexia, headache, venous and arterial thromboses, hypertension, cough, rash, arthralgia, bone pain, myalgia, pain in extremities, chills, influenza-like illness, injection site reaction, and peripheral oedema2.

INNOVATION and/or ADVANTAGES

If licensed, epoetin alfa will offer an additional treatment option for patients with anaemia associated with MDS.

DEVELOPER

Janssen-Cilag Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

MDS are a heterogeneous group of haematological diseases that are characterised by a unil- or multilineage dysplasia of bone marrow stem cells3. These dysplasias typically result in anaemia, leukopenia or thrombopenia due to ineffective haematopoiesis, but leucocytosis or thrombocytosis may also occur4,5. MDS affect patients’ quality of life due to debilitating symptoms such as fatigue and dyspnoea, treatment regimens involving hospitalisation with intravenous drug infusions and blood transfusions, and complications such as severe infections6. In higher-risk MDS there is an increased risk of transformation into acute myeloid leukaemia (AML)7. Recently, MDS with 20-30% blood or bone marrow blasts were
Horizon Scanning Research & Intelligence Centre

reclassified as AML with myelodysplastic features\(^a,\(^8\). Prognosis of MDS is determined by the International Prognostic Scoring System (IPSS), which characterises outcome as low risk, intermediate-1 risk, intermediate-2 risk or high risk for both overall survival and AML progression. IPSS parameters include the proportion of blasts, bone marrow cytogenetic findings, and the number of blood cytopenias\(^6\). Patients with higher risk MDS have a 33-45% chance of AML transformation overall\(^9\). Expert opinion notes that although the IPSS has been superseded as a prognostic system for untreated patients by the revised IPSS (IPSS-R), all current therapeutic algorithms were derived using IPSS\(^8\).

The cause of MDS is known in only 15% of cases. The disorder shows a slight male predominance except for the form with an isolated 5q deletion, in which women predominate\(^10\). Environmental risk factors include previous use of chemotherapy, especially of alkylating agents and purine analogues, radiotherapy, and tobacco smoking\(^10\). Recognised occupational factors include exposure to benzene and its derivatives\(^10\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

The annual incidence of MDS is estimated at 4 per 100,000, but incidence increases with age, and is 30 per 100,000 per year in people over 70 years of age\(^6\). In 2013, there were 2,335 people newly diagnosed with MDS in England, with over 92% of patients aged over 60 at the time of diagnosis\(^11\). Low risk and intermediate-1 risk MDS together form approximately 70% of all MDS\(^6\). Most patients with MDS will be anaemic at some stage; 40% at diagnosis and 80% during the course of their disease\(^12\).

The company states that in more than two thirds of MDS cases, anaemia is present at diagnosis. Improving erythropoiesis, and thus eliminating fatigue and symptoms, is the main therapeutic target for the majority of patients with MDS, as >50% present with anaemia with haemoglobin levels <10g/dL. A significant proportion of patients (around 85%) develop more serious anaemia as MDS progresses and >80% require red blood cell transfusion at some point in their disease\(^b\).

In patients with low to intermediate-1 risk MDS, approximately 50% of elderly patients die from causes other than the consequences of MDS or AML\(^4\). Patients with low to intermediate-1-risk MDS have a median survival of around 3-6 years without intervention\(^10\). In England and Wales, 1,070 deaths from MDS were registered during 2014 (ICD-10 D46)\(^13\). In the same year, there were 53,750 admissions for MDS (ICD-10 D46) in England, resulting in 24,200 bed-days and 55,140 finished consultant episodes\(^14\).

The population likely to be eligible to receive epoetin alfa could not be estimated from available published sources.

\(^a\) Expert personal communication.
\(^b\) Company provided information.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance


CURRENT TREATMENT OPTIONS

Treatment options for MDS are dependent on IPSS risk category. In addition, age and performance status are also critical determinants because they have a major influence on the patient’s ability to tolerate intensive treatments. In lower risk MDS, the main priority is generally the treatment of cytopaenias, mainly anaemia, and the improvement of quality of life. In patients with lower risk MDS without 5q deletion, erythropoietin-stimulating agents (ESA) such as recombinant EPO or darbepoetin (used off-label), remain the first choice of treatment for anaemia. Anaemia associated with lower risk MDS with 5q deletion, compared with that of other lower risk MDS, shows lower response rates and significantly shorter responses to ESA.

Expert opinion states that recombinant EPO has been widely used in the treatment of MDS for a number of decades, both in the form of epoetin alfa (Eprex) and darbopoetin (Aranesp), with the latter generally being preferred by clinicians. Long-term treatment with ESA is recommended in patients who achieve an erythroid response and therefore become independent of red blood cell transfusions. In patients with sideroblastic forms of MDS (refractory anaemia with ring sideroblasts and multilineage dysplasia) granulocyte-colony stimulating factor (G-CSF) is recommended alongside ESA. Expert opinion also notes that factors predictive of response to ESA are well established, with models predicting response rates from 7% to 74%. Factors predicting highest response rates are low endogenous EPO concentrations and a low transfusion burden.

Treatment after ESA failure (primary resistance or relapse after a response) in patients who remain with IPSS low or intermediate-1 MDS is still disappointing overall, with most patients eventually becoming dependent on red blood cell transfusions in the long-term.

Expert personal communication.
## EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01381809, CR018367, EPOANE3021, 2010-022884-36; epoetin alfa vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Janssen-Cilag Ltd.</td>
</tr>
<tr>
<td>Status</td>
<td>Complete but unpublished.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry¹, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK).</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=130; MDS; low- or intermediate-1-risk disease; haemoglobin ≤10g/dL; serum erythropoietin &lt;500mU/mL; ≤4 red blood cell transfusion units over the previous 8 wks; no anaemia attributed to factors other than MDS; no secondary MDS arising after chemotherapy, immunotherapy or radiation therapy or exposure; no prior therapy with any erythropoiesis-stimulating agent.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to epoetin alfa 337.5 - 1,050IU/kg SC once wkly for 24 to 48 wks; or placebo SC once wkly for 24 to 48 wks.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 24 to 48 wks.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Erythroid response.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Maintenance of erythroid response, duration of response, time to first red blood cell transfusion, transfusion-free intervals, number of red blood cell units transfused, quality of life as measured by Functional Assessment of Cancer Therapy-Anaemia/Fatigue (FACT-An) score and EuroQol 5-dimension (EQ-5D) score, duration of hospitalisation, number and duration of medical care encounters.</td>
</tr>
<tr>
<td>Key results</td>
<td>For epoetin alfa vs placebo, respectively: erythroid response at any time during first 24 wks, 31.8% vs 4.4%; erythroid response at wk 24, 27.1% vs 2.2%; mean erythroid response duration, 192.3 days vs 99.0 days; time to first red blood cell transfusion, 49 days vs 37 days; mean number of transfusion-free days, 212.4 days vs 176.1 days.</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>At least one treatment-emergent AE was experienced by 77.6% of epoetin alfa group and 88.0% of placebo group. At least one serious treatment-emergent serious AE was experienced by 25.9% of epoetin alfa group and 17.8% of placebo group. The two treatment-emergent serious AE in the epoetin alfa group were embolism (distal deep venous thrombosis) and development of anti-erythropoietin antibodies.</td>
</tr>
</tbody>
</table>

## ESTIMATED COST and IMPACT

### COST

Epoetin alfa (as Eprex) is already marketed in the UK; the list price for 1 pre-filled syringe (40,000IU/1mL) costs £265.48, and treatment with 337.5 - 1,050IU/kg once weekly would cost £10,354-27,610 per year.¹⁶ Assumed an average weight of 77.5kg (Health Survey for England 2014). However, the company report that Eprex is subject to a national tendering process and the eMit price will apply to its use.
Impact on Patients and Carers

✔ Reduced mortality/increased length of survival: expert opinion notes that preliminary data may suggest that EPO, if introduced early following diagnosis, may be associated with a marginal survival benefit.

✔ Reduced symptoms or disability: expert opinion notes that the main advantage of EPO treatment in patients who respond is that they do not require red blood cell transfusions and tend to maintain a stable haemoglobin level, rather than the peaks and troughs observed in transfusion-dependent patients, which relieves symptom burden. The company states that epoetin alfa will be used to alleviate fatigue and symptoms in patients with anaemia, and to delay time to red blood cell transfusion which may be associated with iron overload, fluctuating and/or persistently low haemoglobin levels (usually <10g/dL), in addition to the risks related to intolerance reactions, allo-immunisations, and infections.

☐ Other

Impact on Health and Social Care Services

☐ Increased use of existing services

✔ Decreased use of existing services: expert opinion states that if patients do become transfusion independent, this may represent an overall cost saving given the reduction in transfusion costs, nursing time, blood bank time and day unit bed time. Responding patients will also avoid risks of iron overload so there may be a savings in terms expensive iron chelation drugs.

☐ Re-organisation of existing services

✔ Other: uncertain unit cost compared to existing treatments.

☐ Need for new services

☐ None identified

Impact on Costs and Other Resource Use

☐ Increased drug treatment costs

✔ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

✔ Other: expert opinion notes that most units will tender for the cheapest EPO product. Whether there will be an uplift in cost for the NHS will depend upon commissioners view regarding how essential it will be to purchase Exprex.

☐ None identified

Other Issues

☐ Clinical uncertainty or other research question identified

✔ None identified

* Expert personal communication.

† Company provided information.
REFERENCES


