

**NIHR Innovation Observatory
Evidence Briefing: August 2017****Darbepoetin alfa (Aranesp) for treatment of
anaemia in adults with low or intermediate-1-risk
myelodysplastic syndromes**

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LAY SUMMARY

Myelodysplastic syndromes (MDS) are a group of blood disorders, in which the bone marrow does not produce enough healthy red blood cells, white blood cells and/or platelets. Faulty cells often die earlier than normal cells and the body destroys some abnormal cells, leaving the patient with low blood counts. This can result in anaemia (not enough haemoglobin or fewer red blood cells). MDS usually occurs in people older than 65 years. Symptoms include tiredness, unusual bleeding or being short of breath. MDS can occur because of genetic syndromes, smoking, or as a treatment-related MDS after cancer therapy.

Darbepoetin alfa may, if licensed, reduce the incidence of red blood cell transfusions in anaemic patients with low and intermediate-1 risk MDS and improve quality of life.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Treatment of anaemia in adult patients with low or intermediate-1-risk myelodysplastic syndromes (MDS)

TECHNOLOGY

DESCRIPTION

Darbepoetin alfa (Aranesp) is a recombinant human protein agonist of the erythropoietin receptor.¹ Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. Erythropoietin interacts with progenitor stem cells to increase red blood cell production. Binding of erythropoietin to the erythropoietin receptor leads to receptor dimerization, which facilitates activation of JAK-STAT (Janus kinase - signal transducers and activators of transcription) signalling pathways within the cytosol. Activated STAT proteins are then translocated to the nucleus where they serve as transcription factors which regulate the activation of specific genes involved in cell division or differentiation. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red blood cell (RBC) production. Increased haemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with darbepoetin alfa.²

This product is licensed in the EU for anaemia in chronic kidney disease (renal anaemia) and chemotherapy induced anaemia.²

In the phase III clinical trial, participants received darbepoetin alfa administered as subcutaneous injection, 500 µg every three weeks (Q3W) for 24 weeks in the double-blind treatment period, and continued to receive darbepoetin alfa, 500 µg Q3W, during the active treatment period for an additional 48 weeks.³

INNOVATION and/or ADVANTAGES

If licensed, darbepoetin alfa will offer an additional treatment option for adults with low or intermediate-1-risk myelodysplastic syndromes. The company states that darbepoetin alfa reduces the incidence of red blood cell transfusions in anaemic patients with low and intermediate-1-risk MDS, as well as improving erythroid response.⁴

DEVELOPER

Amgen Ltd

PATIENT GROUP

BACKGROUND

Myelodysplastic syndromes (myelodysplasia) (MDS) is a blood disorder that causes a drop in the number of healthy blood cells. Whereas bone marrow usually produces red blood cells, white blood cells and platelets, in MDS bone marrow produces abnormal cells that are not fully developed.⁸ Hence,

MDS refers to a collection of hematologic malignancies that share an ineffective production (haematopoiesis) of normal bone marrow or myeloid cells. Disease-related anaemia (not enough haemoglobin or fewer red blood cells⁵) can often lead to complications.⁶ Defective cells often die earlier than normal cells and the body destroys some abnormal body cells, leaving the patient with low blood counts.⁷ Three main types of MDS exist: refractory anaemia, where only the red blood cells are affected; refractory cytopenia, in which the red and white blood cells and platelets are affected; and refractory anaemia with excess blasts (RAEB), which affects red and white blood cells and platelets as well as involving a higher risk of developing acute myeloid leukaemia (AML).⁸

Myelodysplastic syndrome (ICD code D46.0-46.9⁹) is a type of cancer and usually occurs in people over 65, but can also impact younger people. Symptoms might not be apparent at an early stage of the disease, however as disease progresses, they include constant tiredness, unusual bleeding, bruises and tiny red marks under the skin, paleness and shortness of breath.¹⁰ The main risk factor for MDS is cancer treatment. Patients who get treated with certain chemotherapy drugs for cancer are more likely to develop MDS. Other risk factors include genetic syndromes, familial MSD, smoking, or exposure to radiation⁷. Treatment-related MDS, such as after cancer therapy, can occur 1 to 15 years after receiving chemotherapy or radiation.¹⁰

CLINICAL NEED and BURDEN OF DISEASE

According to NICE, 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, and many cases remain undiagnosed. Around 30% of people with MDS will progress to acute myeloid leukaemia. Median survival with low risk and intermediate-1 risk MDS is 5.7 years and 3.5 years respectively.¹¹ There is a higher prevalence in males than in females. Children are rarely affected by this disease. An increase in secondary MDS numbers is to be expected due to a higher number of previous chemotherapy and radiotherapy that patients receive to treat other malignancies.¹²

According to the latest Hospital Episode Statistics for England in 2015-16 there were 55,966 finished consultant episodes (FCEs) reported for MDS as well as 54,509 hospital admissions. Of the FCEs, 36,612 were in male patients and 19,354 in female patients.¹³

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality (TA322). September 2014
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016
- NICE guideline. Chronic kidney disease: managing anaemia (NG8). June 2015

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P. February 2017

OTHER GUIDANCE

Giraldo P, Nomdedeu B, Loscertales J et al. Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. *Cancer* 107:12, Nov 2006. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/cncr.22343/pdf> [Accessed 04 Aug 2017]

Stasi R, Abruzzese E, Lanzetta G, Terzoli E, Amadori S. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. *Annals of Oncology*, 16 (2005) 12: 1921-1927. Available from: <https://academic.oup.com/annonc/article/16/12/1921/225709/Darbepoetin-alfa-for-the-treatment-of-anemic> [Accessed 04 Aug 2017]

CURRENT TREATMENT OPTIONS

Due to a wide variation in clinical presentation treatment strategies are confounded and development of new therapies has been hindered. However, improved classification and prognostic systems are providing a more refined stratification of patients, which help to guide treatment and management decisions. Patients who are classified with International Prognostic Scoring System as low- and intermediate-1 (Low/Int-1) risk are considered to have low-risk MDS. These patients are primarily treated with low-intensity supportive care. They receive red blood cell transfusions to treat symptoms and maintain quality of life. Hematopoietic cytokines or antithymocyte globulin may reduce transfusion requirement.¹⁴ The use of growth factors intensifies therapy with allogeneic hematopoietic stem cell transplantation (HSCT).⁶

The choice of treatment should depend on the patient's age, performance status, and Myelodysplastic Syndrome International Prognostic Scoring System (IPSS). In patients with lower risk MDS the main goal is to provide symptom control and to improve quality of life. Treatment for this patient group is indicated if there is a symptomatic anaemia, thrombocytopenia or recurrent infections in the setting of neutropenia. Lower-risk patients, who may be dependent on blood product transfusions, may derive some benefit from the use of growth factors. Recombinant human erythropoietin (rhEPO) or darbepoetin are used initially as single agents¹⁵ to relieve anaemia and reduce transfusion requirements.¹⁶ Less intensive therapeutic options include the use of lenalidomide or immunosuppressive therapy. Azacitidine and decitabine are FDA approved therapies usually used to treat higher risk MDS.⁶ Stem cell transplant is the only treatment to actually cure MDS. Stem cells, coming from either donor bone marrow or blood, will be used after destroying abnormal cells through chemotherapy or radiation.¹⁰

EFFICACY and SAFETY

Trial	NCT02175277, EudraCT-2013-000727-13, MDS 20090160, Darbepoetin Alfa MDS Companion Protocol
Sponsor	Amgen Ltd
Status	Complete but unpublished.
Source of Information	Trial registry ¹⁷
Location	Belgium
Design	Non-randomized, uncontrolled
Participants	N=9 (planned); ¹⁸ Subjects that complete the active-treatment period of the darbepoetin alfa MDS 20090160 study and meet the eligibility criteria may be

	enrolled into this study to continue treatment of darbepoetin alfa for up to 73 weeks or until progression to acute myelogenous leukaemia (AML), whichever occurs first
Schedule	Darbepoetin alfa will be given at 500 µg three-times per week/two-times per week. The first dose and dosing frequency on day 1 / week 1 should carry forward from the last dose and frequency from the parent study (darbepoetin alfa MDS 20090160 study) administered at week 70 / 71. The day 1 / week 1 visit should align within +10 days of the End of Active Treatment Period (EOATP) visit at week 72 / 73 from the darbepoetin alfa MDS 20090160 study. The investigator may choose to increase the dose of darbepoetin alfa with the maximum dose permitted of 500 µg two-times per week. Dose increases should follow a step-wise approach, (eg, 300 µg to 500 µg; 200 µg to 300 µg) with at least 8 weeks at a given dose before the dose may be increased.
Follow-up	Not reported
Primary Outcomes	Subject incidence of treatment-emergent adverse events
Secondary Outcomes	Disease progression to acute myeloid leukaemia (AML); mortality
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Not reported

Trial	NCT01362140, EudraCT-2009-016522-14, Darbepoetin Alfa in Patients with Anaemic Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)
Sponsor	Amgen Ltd
Status	Ongoing
Source of Information	Trial registry ³
Location	9 EU countries
Design	Randomised, placebo-controlled
Participants	N=146; aged ≥18 years; Low or intermediate-1 risk MDS patients as per International Prognostic Scoring System (IPSS); World Health Organization (WHO) classification of refractory anaemia (RA), refractory anaemia with ring sideroblasts (RARS), refractory cytopenias with multilineage dysplasia (RCMD), MDS-unclassified (MDSU), MDS with isolated del(5q) (5q- syndrome) or refractory anaemia with excess blasts-1 (RAEB-1); Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 assessed during screening
Schedule	Participants received darbepoetin alfa 500 µg every three weeks (Q3W) for 24 weeks in the double-blind treatment period, and continued to receive darbepoetin alfa 500 µg Q3W during the active treatment period for an additional 48 weeks
Follow-up	Long-term follow-up (LTFU) will occur every 26 weeks (± 4 weeks) from the EOATP visit (or EOTP visit if the participant does not enter the active treatment period) and will continue for a minimum of 3 years from the first dose of IP. Follow-up may occur through clinic visit or telephone contacts. Information on the participant's survival and progression to AML status will be collected during LTFU

Primary Outcomes	Percentage of participants with at least one red blood cell transfusion during the double-blind treatment period	
Secondary Outcomes	Percentage of participants who achieved an erythroid response based on International Working Group (IWG) 2006 criteria in the double-blind treatment period; number of participants with adverse events	
Key Results	RBC transfusions during 24 week double blind dosing: 36.1% darbepoetin alfa vs. 59.2% Erythroid response during 24 week double blind dosing: 14.7% darbepoetin alfa vs. 0%	
Adverse effects (AEs)	During 24 week double blind dosing	
	Placebo (N=48)	Darbepoetin alfa (N=98)
	≥ grade 3 AE	27%
	≥ grade 4 AE	13%
	Serious AE	17%
	Progression to AML	25
Expected reporting date	-	

ESTIMATED COST and IMPACT

COST

Darbepoetin alfa is already marketed in the UK for other indications; 1 pre-filled syringe for injection with 500 micrograms/1ml solution of darbepoetin alfa costs £734.05 in the UK (list price).¹⁹

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services (likely to result in reduced blood transfusion requirements) |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

INFORMATION FROM

Amgen Ltd

UK PharmaScan ID number 645505.

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