Title of the program	A Medical Need Program of Darbepoetin Alfa for the Treatment of Anemic Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS)
Product Name	Aranesp®
Active substance	Darbepoetin alfa
Indication	<u>Intended Indication for this Medical Need Program</u> Darbepoetin Alfa for the Treatment of Anemic Patients with Low or Intermediate-1 Risk MDS <u>Authorized Indication</u> Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. <u>Rationale for this program</u> A multicenter phase 3, randomized, double-blind, placebo-controlled study of darbepoetin alfa for the treatment of anemic subjects with low or intermediate-1 risk MDS (NCT01362140 - Arcade trial)
In- and exclusion criteria	<u>Inclusion Criteria:</u> - The patient has been included in the MDS 160 study and has responded to darbepoetin alfa treatment Or - All of following: • Adults of 18 years of age or older and subject or subject's legally acceptable representative has provided informed consent • World Health Organization (WHO) classification of refractory anaemia (RA), refractory anaemia with ring sideroblasts (RARS), refractory cytopenias with multilineage dysplasia (RCMD), MDS-unclassified (MDS-U), MDS with isolated del(5q) (5q- syndrome) or refractory anaemia with excess blasts-1 (RAEB-1) • Low or intermediate-1 risk MDS patients per IPSS at the time of inclusion, as determined by complete blood count (CBC) , bone marrow examination and marrow cytogenetic analysis • Patient with symptomatic anemia and Hemoglobin level ≤ 10.0 g/dL • Patient is not transfusion dependant (i.e. ≤ 2 units of RBC needed per month – in the months previous to program submission) • Adequate Performance Status (Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1) Iron stores, vitamin B12 status and serum- or RBC- folate levels considered adequate by the treating physician • Endogenous EPO level of < 500 U/l - In both cases: Written informed consent should be obtained prior to requesting the medication from the subject or from the subject's legally acceptable representative
Treatment	<u>Treatment</u> - The suggested standard starting dose is 500 µg subcutaneously every 3 weeks (500 µg Q3W). - In case of adequate response to therapy – determined at the discretion of the treating physician – further requests of the necessary product forms and quantity can be issued, and product supply will be provided for further treatment periods of approximately 2 months per request. - In case of inadequate response after the initial treatment period, inadequate Hb stabilization after prior response to darbepoetin alfa, or in case of progression of the underlying disease, the treatment should be discontinued at the initiative of the treating physician. Any unused product needs to be returned to Amgen. <u>Dose reduction and stopping rules</u> - Exceeding the hemoglobin level threshold: If at any time during the program the haemoglobin reaches > 12.0 g/dL, darbepoetin alfa dosing should be temporarily withheld until the hemoglobin level is ≤ 11.0 g/dL at which time treatment can be reinitiated at a reduced intensity (500µg to 300µg, maintain previous dosing frequency). - If haemoglobin increases by > 1.5 g/dL in any 21-day period for Q3W dosing or > 1.0 g/dL in any 14-day period for Q2W dosing in the absence of RBC transfusion, the dose will be reduced from the previous dose (ie, 500 µg to 300 g) (maintain previous dosing frequency of Q3W or Q2W). - Darbepoetin alfa will be discontinued after 3 dose reductions

	- Related Adverse Event: If at any time during the program a patient experiences a severe or life-threatening adverse event considered by the investigator to be related to the product, administration of darbepoetin alfa will be permanently stopped. All adverse events need to be reported to Amgen without any delay. - Thrombotic Event: If at any time during the program a patient experiences a grade 3 or 4 thrombotic event according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, administration of the product will be permanently stopped. <u>Dose Escalation</u> If a patient does not maintain a hemoglobin level of > 11.0 g/dL at a specific dose intensity (calculated average dose per week), the dose intensity may be increased to a higher level, however never exceeding a maximum dose intensity of 300µg per week. As soon as the patient experiences a Hb level higher than 12.0 g/dL, the dose intensity needs to be reduced to a lower level, aiming to reach a minimal dose to stable Hb levels between 11.0 and 12.0 g/dL for the individual patient. If a patient has a haemoglobin increase of < 1.5 g/dL (in the absence of RBC transfusion in the prior 28 days), the dose is escalated (eg, from 500 µg Q3W to 500 µg Q2W) If the dose is adjusted to Q2W, the Q2W dose frequency is then maintained, even if the dose is later reduced.
Process to include a patient	<u>Inclusion of a patient</u> 1. Completed and signed ICF 2. Login via online platform www.mnparanespinmds.com with personal login details. (login can be requested via Amgen contact persons; see below) 3. Review by 3 BHS physicians 4. If positive advise: confirmation of enrolment by the responsible physician of the program 5. All requests will be treated as soon as possible, and at the latest within 10 working days after the request. Darbepoetin alfa will be provided after confirmation of the request by the responsible physician. The need for up to additional treatment cycles is patient-dependent and will be determined by the treating physician. **Protocol and ICF can also be found on the online platform under "documents".** <u>Product Supply:</u> - Aranesp® 500 or Aranesp® 300 will be provided as prefilled syringes (PFS) or as prefilled pens (SureClickTM), at the choice and preference of the requesting physician. - After each approved request for product supply, and depending on the preferred dosage form and frequency of injections requested, an adequate number of Aranesp® 500 or 300 µg units will be provided for an initial treatment period of 8 to 9 weeks per individual patient included in this medical need program.
Duration of the program	This program started after its approval by the Belgian authorities (FAMHP) in Belgium and by the Ministry of Health of Luxembourg in Luxembourg. The MNP will be ended if one of the following criteria is met: • Darbepoetin alfa is available in the indication of treatment of Low risk or Intermediate-1 risk MDS, following reimbursement approval • EMA ultimately decides that the benefit/risk assessment is not supportive of registration of darbepoetin alfa in this indication • Amgen decides to withdraw the registration dossier following an unfavorable benefit/risk profile or unfavorable results of the ongoing phase 3 study of darbepoetin alfa in Low risk or Intermediate-1 risk MDS • Amgen decides to stop the development of darbepoetin alfa in this indication. Under these conditions, the Belgian law regarding MNP would not allow the continuation of this program. Enrolment of new patients after the originally planned duration of this medical need program won't be possible anymore.
Responsible of the program	<u>Responsible of the program:</u> Amgen N.V. / S.A. Arianelaan 5 1200 Brussels Phone: +32 2 775 27 11 <u>Responsible physician:</u> Dr. Jo Van der Veken <u>Points of contact for this program:</u>

	- Dr. Sofie Vingerhoedt Sr. Medical Advisor +32 (0)2 775 28 60 +32 (0)476 33 96 18 sofiev@amgen.com - Ann Curias Regional medical liaison +32 (0)476 39 70 75 acurias@amgen.com
Modalities for the disposal	Any unused or expired medication needs to be returned to Amgen or destroyed in an appropriate facility as soon as possible after the patient's discontinuation from the compassionate use program. The medication delivered for an individual patient request in the context of a medical need program can only be used for that particular patient.
The information for registration of suspected unexpected serious adverse reactions	Physicians are requested to report all adverse events (non-serious and serious), other safety findings and product complaints by OR faxing a completed, signed and dated Safety Report Form to the Amgen – Belgian Safety Department (Safety fax nr: 0800 80 877) within one working day OR mailing a completed, signed and dated Safety Report Form to the email svc-ags-in-be@amgen.com within one working day. The physician may be asked to provide follow-up information on the reported event. In case of an adverse event, the treating physician will decide on the further treatment with darbepoetin alfa, and on the actions needed to take.