Report REBLOZYL ® - Luspatercept

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Luspatercept **Brand Name:** Reblozyl **Originator/licensee:** Bristol Myers Squibb Pharma EEIG **Classification:** NI **ATC code:** B03XA06 **OrphanStatus:** **Eu:** Yes **Us:** Yes **Mechanism of action:** Luspatercept, regulates the maturation of red blood cells by blocking a signalling pathway called Smad2/3, that slows down the maturation of red blood cells and is overactive in pts with beta thalassaemia and myelodysplastic syndromes. Blocking Smad2/3 increases the production of red blood cells and allows them to develop normally. [1]	**Authorized Indication:** **EMA:** Luspatercept is indicated for the treatment of pts with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS).[2] **FDA:** Luspatercept is indicated for the treatment of anemia in adult patients with very low- to intermediate-risk MDS-RS or with MDS/MPN-RS-T. [3] **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:**22/02/2024 **FDA M.A. date:**03/04/2020 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No --- **ABBREVIATIONS:** **AE:** adverse event **CHMP:** Committee for Medicinal Products for Human Use **ESA:** erythropoiesis-stimulating agent **IPSS-R:** International Prognostic Scoring System-Revised **M.A.:** Marketing Authorization **MDS:** myelodysplastic syndromes **MDS-RS:** myelodysplastic syndromes with ring sideroblasts **MDS/MPN-RS-T:** myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis **P.O.:** Positive Opinion **Pts:** patients **RBC:** red blood cell **RBCTI:** red blood cell transfusion independent	**Summary of clinical EFFICACY:** **MEDALIST(NCT02631070):**is a phase III, multicenter, randomized, double-blind, placebo-controlled trial in pts with IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes who have ring sideroblasts and require red blood cell transfusions (two or more RBC units over eight weeks). For eligibility, pts were required to have had an inadequate response to prior treatment with an ESA, be intolerant of ESAs, or have a serum erythropoietin > 200 U/L. The trial excluded pts with deletion 5q (del 5q), white blood cell count > 13 Gi/L, neutrophils < 0.5 Gi/L, platelets < 50 Gi/L, or with prior use of a disease modifying agent for treatment of MDS. The trial included 229 pts randomized 2:1 to luspatercept (n=153) or placebo (n=76). Randomization was stratified by baseline RBC transfusion burden and baseline IPSS-R. Treatment was started at 1 mg/kg subcutaneously every three weeks; dose could be increased after completion of the first two cycles, if the pt had at least one RBC transfusion in the prior six weeks. Two dose level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg). Doses were held and subsequently reduced for AEs, reduced if the hemoglobin increased by ≥ 2 g/dL from the prior cycle, and held if the pre-dose hemoglobin was ≥ 11.5 g/dL. The efficacy of luspatercept in adult pts with MDS-RS and MDS-RS-T was established based upon the proportion of pts who were RBC-TI, defined as the absence of any RBC transfusion during any consecutive 8-week period occurring entirely within weeks 1 through 24. [3] Of the 229 pts enrolled, 153 were randomly assigned to receive luspatercept and 76 to receive placebo; the baseline characteristics of the patients were balanced. Transfusion independence for eight weeks or longer was observed in 38% of the pts in the luspatercept group, as compared with 13% of those in the placebo group (P<0.001). [7] **Summary of clinical SAFETY:**The safety of luspatercept at the recommended dose and schedule was evaluated in 242 pts with MDS with ring sideroblasts (n=192) or other myeloid neoplasms (n=50). The safety population included 63% males and 37% females of median age 72 years (range, 30 – 95 years); of these pts, 81% were White. The median time on treatment with luspatercept was 50.4 weeks (range, 3 – 221 weeks); 67% of ptswere exposed for six months or longer and 49% were exposed for greater than one year. Among the 242 pts treated with luspatercept, 5 (2.1%) had a fatal adverse reaction, 11 (4.5%) discontinued due to an adverse reaction, and 7 (2.9%) had a dose reduction due to an adverse reaction. The most common (>10%) all-grade AEs included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. The most common (>2%) Grade > 3 adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. [3] **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes **Discontinued studies (for the same indication):**- --- **References:** [1] https://www.ema.europa.eu/en/documents/overview/reblozyl-epar-medicine-overview_en.pdf [2] https://www.ema.europa.eu/en/medicines/human/variation/reblozyl [3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761136orig2lbl.pdf [4] https://gallery.farmadati.it/Home.aspx [5] https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/8558-Luspatercept-for-MDS-associated-anaemia-V1.0-SEP2018-NONCONF.pdf [6] https://www.nejm.org/doi/10.1056/NEJMoa1908892?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed [7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7846829/	**Cost of therapy:**a vial of Reblozyl SC, 25 mgcosts €1,333.90(ex-factory price) [4]. **Epidemiology:**The incidence of MDS in the EU has been approximated at 4 pts per 100,000 people (reaching 40–50/100,000 in subjects aged ≥70 years). [5] **POSSIBLE PLACE IN THERAPY**:For the treatment of dependent transfusion anaemia caused by MSD, therapy is customized according to the pts characteristics.Currently, the most common therapeutic approaches include:Erythropoiesis-stimulating agents as a first-line treatment for lower-risk myelodysplastic syndromes. [6] Hypomethylating agents, Azacitidine (Vidaza®) and Decitabine (Dacogen®), for pts who have not responded to any other treatment. Lenalidomide that has shown efficacy in treating certain types of lower-risk MDS with a deletion of chromosome 5q (del[5q])[7] Luspatercept may offer a novel treatment option for adult patients with very low, low and intermediate risk MDS associated anaemia and who are RS+ and require RBC transfusions and have received or are not eligible for ESA therapy. [5] **OTHER INDICATIONS IN DEVELOPMENT:(NCT05664737)** Anemia, **(NCT06254781)** Adult Granulosa Cell Tumor of Ovary. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**:- **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:**Yes *Service reorganization: No *Possible off label use: Yes