Prescribing Information

Zynteglo▼ (betibeglogene autotemcel)

Please refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation**: 1.2-20 × 10^6 cells/mL dispersion for infusion. **Indication:** Treatment of patients ≥12 years with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. **Dosage:** The finished product is composed of one or more infusion bags which contain a dispersion of 1.2-20 × 10^6 cells/mL suspended in cryopreservative solution. Each infusion bag contains approximately 20 mL of Zynteglo. Minimum recommended dose of Zynteglo is 5.0 × 10^6 $CD34^+$ cells/kg. In clinical studies doses up to 20 × 10^6 $CD34^+$ cells/kg have been administered. Quantitative information regarding strength, $CD34^+$ cells, and dose is provided in the Lot Information Sheet. **Administration:** Zynteglo must be administered in a qualified treatment centre by a physician(s) with experience in HSC transplantation and treatment of patients with TDT. Zynteglo is intended for autologous use and should only be administered once. *Mobilisation and apheresis:* HSC mobilisation followed by apheresis to obtain $CD34^+$ stem cells which will be used for medicinal product manufacturing is required. Minimum target of $CD34^+$ cells collected is 12 × 10^6 $CD34^+$ cells/kg. Back-up collection ≥1.5 × 10^6 $CD34^+$ cells/kg (if collected by apheresis) or >1.0 × 10^8 TNC/kg (if collected by bone marrow harvest) is required. *Pre-treatment conditioning:* Full myeloablative conditioning must be administered before infusion of Zynteglo and only when the complete set of infusion bag(s) constituting Zynteglo dose is received and stored at administration site, and availability of back-up collection is confirmed. Prophylaxis for veno-occlusive liver disease is recommended. It is recommended that patients maintain haemoglobin ≥11 g/dL for ≥30 days prior to mobilisation and during conditioning. Iron chelation should be stopped ≥7 days prior to conditioning. *Zynteglo administration:* For intravenous use only. After completion of the 4-day course of myeloablative conditioning, there must be a minimum of 48 hours of washout before Zynteglo infusion. Before infusion, confirm that the patient's identity matches the unique patient information on the Zynteglo infusion bag(s). The total number of infusion bags should be confirmed with the Lot Information Sheet. Complete Zynteglo infusion as soon as possible and ≤4 hours after thawing. Each infusion bag should be administered in <30 minutes. *After Zynteglo administration:* Any blood products required within the first 3 months after Zynteglo infusion should be irradiated. **Special populations***: Elderly:* Zynteglo has not been studied in patients >65 years of age. *Renal impairment:* Zynteglo has not been studied in patients with renal impairment. Assess patients for renal impairment (creatinine clearance ≤70 mL/min/1.73 m^2) to ensure HSC transplantation is appropriate. No dose adjustment is required. *Hepatic impairment:* Zynteglo has not been studied in patients with hepatic impairment. Assess patients for hepatic impairment to ensure HSC transplantation is appropriate. *Paediatric population:* Safety and efficacy of Zynteglo in children <12 years of age have not yet been established. *Patients seropositive for human immunodeficiency virus (HIV) or human T-lymphotropic virus (HTLV):* Zynteglo has not been studied in patients with HIV-1, HIV-2, HTLV-1, or HTLV-2. Negative HIV serology test necessary to ensure acceptance of apheresis material for Zynteglo manufacturing.

Contraindications: Hypersensitivity to active substance or excipients (Cryostor CS5, sodium chloride). Pregnancy and breast-feeding. Previous treatment with HSC gene therapy. Contraindications to the mobilisation agents and the myeloablative conditioning agent must be considered. **Warnings and Precautions:** Traceability: Requirements of cell-based advanced therapy medicinal products must apply. Name of the product, batch number and name of the treated patient should be kept for 30 years. General: Warnings and precautions of mobilisation agents and myeloablative conditioning agent must be considered. Patients treated with Zynteglo should not donate blood, organs, tissues or cells. Risks associated with TDT and iron overload: HSC transplantation with myeloablative conditioning is not appropriate for patients with cardiac T2* <10 msec by magnetic resonance imaging (MRI). Liver MRI should be performed prior to myeloablative conditioning. If MRI results demonstrate liver iron content ≥15 mg/g, liver biopsy should be performed. In patients with bridging fibrosis, cirrhosis, or active hepatitis, HSC transplantation with myeloablative conditioning is not appropriate. Risk of insertional oncogenesis: Monitor annually for leukaemia or lymphoma (including complete blood count) for 15 years post treatment. Serological testing: Test for HIV-1/2 prior to mobilisation and apheresis. Interference with serology testing: Do not screen Zynteglo treated patients for HIV using PCR-based assay due to risk of false positive. Engraftment failure as measured by neutrophil engraftment: Patients who experience neutrophil engraftment failure should be managed with rescue treatment from back-up collection. Delayed platelet engraftment: Patients should be made aware of bleeding risk until platelet recovery achieved. Monitor for thrombocytopenia and bleeding according to standard guidelines. Platelet counts should be monitored according to medical judgment until platelet engraftment and platelet recovery are achieved. Anti-retroviral and hydroxyurea use: Anti-retroviral medications and/or hydroxyurea should be stopped ≥1 month prior to mobilisation until ≥7 days after Zynteglo infusion. Sodium content: Zynteglo contains 391-1564 mg sodium per dose. **Interactions:** Patients should not take anti-retroviral medicines or hydroxyurea from ≥1 month prior to mobilisation and until ≥7 days after Zynteglo infusion. Interactions between iron chelators and myeloablative conditioning agent must be considered. Iron chelators must be discontinued 7 days prior to initiation of conditioning. Myelosuppressive iron chelators should not be used for ≥6 months after Zynteglo infusion. **Fertility, pregnancy and lactation:** Women of childbearing potential/Contraception in males and females: Women of childbearing potential and men capable of fathering a child must use a reliable method of contraception (intra-uterine device or combination of hormonal and barrier contraception) from start of mobilisation through ≥6 months after administration of Zynteglo. Pregnancy and breast-feeding: Negative serum pregnancy test must be confirmed prior to the start of mobilisation and re-confirmed prior to conditioning and before Zynteglo administration. Zynteglo must not be administered to women who are breast-feeding. Fertility: There are no data on the effects of Zynteglo on human fertility. Data are available on the risk of infertility with myeloablative conditioning. It is advised to cryopreserve semen or ova before treatment if possible. **Effects on ability to drive and use machines:** Zynteglo has no influence on the ability to drive or use machines. The effect of the mobilisation agents and the myeloablative conditioning agent must be considered. **Undesirable Effects:** Very common (≥1/10) adverse drug reactions (ADRs) attributed to mobilisation and apheresis: thrombocytopenia, hypocalcaemia, headache, peripheral sensory neuropathy, nausea, bone pain. Common ADRs (≥1/100 to <1/10) attributed to mobilisation and apheresis: Splenomegaly, leukocytosis, hypokalaemia, hypomagnesaemia, agitation, dizziness, head discomfort, paraesthesia, cardiac flutter, hypotension, hypoxia, epistaxis, vomiting, lip swelling, abdominal pain, abdominal pain

upper, paraesthesia oral, rash, hyperhidrosis, back pain, musculoskeletal discomfort, pyrexia, influenza like illness, chest discomfort, chest pain, injection site reaction, catheter site haemorrhage, catheter site bruise, injection site bruising, fatigue, non-cardiac chest pain, catheter site pain, injection site pain, puncture site pain, pain, blood magnesium decreased, citrate toxicity, contusion, procedural pain. Very common (≥1/10) ADRs attributed to myeloablative conditioning: Veno-occlusive liver disease (serious events in 11.1%), thrombocytopenia, febrile neutropenia, neutropenia, leukopenia, anaemia, vaginal haemorrhage, gingival bleeding, epistaxis, abdominal pain, anal inflammation, constipation, diarrhoea, nausea, stomatitis, vomiting, decreased appetite, insomnia, headache, pharyngeal inflammation, alopecia, pruritus, skin hyperpigmentation, pyrexia, fatigue, mucosal inflammation, alanine aminotransferase increased, aspartate aminotransferase increased and blood bilirubin increased. Common ADRs (≥1/100 to <1/10) attributed to myeloablative conditioning: Neutropenic sepsis, systemic infection, staphylococcal infection, pneumonia, lower respiratory tract infection, urinary tract infection, mucosal infection, cellulitis, vaginal infection, rash pustular, folliculitis, gingivitis, vulvovaginal candidiasis, lymphopenia, leukocytosis, monocyte count decreased, neutrophilia, mean cell haemoglobin concentration increased, primary hypogonadism, hypocalcaemia, hypokalaemia, metabolic acidosis, fluid overload, fluid retention, hypomagnesaemia, hyponatraemia, hypophosphataemia, hyperphosphataemia, anxiety, dizziness, lethargy, dysgeusia, ageusia, memory impairment, conjunctival haemorrhage, vertigo, cardiac failure congestive, atrial fibrillation, hypotension, haematoma, hot flush, hypoxia, pulmonary mass, dyspnoea, pleural effusion, rales, upper-airway cough syndrome, cough, laryngeal pain, hiccups, oropharyngeal pain, anal haemorrhage, gastritis, gastrointestinal inflammation, abdominal distension, abdominal pain upper, anal fissure, dyspepsia, dysphagia, oesophagitis, haemorrhoids, proctalgia, lip dry, cholecystitis, cholelithiasis, hepatomegaly, jaundice, transaminases increased, gamma-glutamyltransferase increased, petechiae, ecchymosis, pain of skin, palpable purpura, pigmentation disorder, pruritus generalised, purpura, sweat gland disorder, urticaria, dry skin, rash, bone pain, myalgia, pain in extremity, back pain, haematuria, pollakiuria, ovarian failure, menstruation irregular, premature menopause, blood follicle stimulating hormone increased, blood testosterone decreased, mucosal inflammation, face oedema, hypothermia, feeling cold, pain, xerosis, C-reactive protein increased, aspergillus test positive, blood potassium decreased, weight decreased, blood alkaline phosphatase decreased, blood magnesium decreased, forced expiratory flow decreased, protein total decreased, blood albumin decreased, reticulocyte count decreased, reticulocyte percentage decreased, transfusion reaction, skin abrasion. Very common (≥1/10) ADRs attributed to Zynteglo: Abdominal pain. Common ADRs (≥1/100 to <1/10) attributed to Zynteglo: thrombocytopenia (serious events in 2.2%), leukopenia, neutropenia, hot flush, dyspnoea, pain in extremity, non-cardiac chest pain. For full safety information, consult the product SmPC

Legal Category: POM

Marketing Authorisation Number: EU/1/19/1367/001. **Cost (excluding VAT):** £1450000

Further information is available from the Marketing Authorisation Holder: bluebird bio (Netherlands) B.V., Stadsplateau 7, WTC Utrecht, 3521AZ Utrecht, The Netherlands **Date of Preparation:** 06 May 2020

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellowcard in the Google Play or Apple App Store. Adverse events should also be reported to bluebird bio at safety.reporting@bluebirdbio.com, or by telephone to 0207 660 0754.