PATIENT IDENTIFICATION

ZYNTEGLO is a one-time gene therapy that expands treatment options for patients with TDT who meet these criteria[1]:

- **Diagnosed with transfusion-dependent β-thalassaemia**
- **NON-β^0/β^0:** do not have a β^0/β^0 genotype
- **≥12 years of age**
- **Appropriate for haematopoietic stem cell transplant**
- **No human leukocyte antigen–matched related donor available**

TREATMENT PARTNERSHIP

Treatment relies on close collaboration

ZYNTEGLO is manufactured and delivered through a highly coordinated and regulated process that involves close collaboration with the referring physician, ZYNTEGLO Qualified Treatment Centre, and bluebird bio.

ZYNTEGLO Qualified Treatment Centres:

If you are considering a patient for ZYNTEGLO, contact a ZYNTEGLO Qualified Treatment Centre to discuss eligibility and next steps.

For additional information on a Qualified Treatment Centre, please contact your local gene therapy representative at bluebird bio.

Abbreviated 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. 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. 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. 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. 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 has 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 HTL-2. Negative HIV serology test necessary to ensure acceptance of apheresis material for Zynteglo manufacturing.

Contraindications: Hypersensitivity to active substance or excipients (Cryostor CS5). 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. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 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. Zynteglo is intended solely for autologous use and must not be administered to other patients. 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 381-1564 mg sodium per dose. **Interactions:** Patients should not take anti-retroviral medicines or hydroxyurea at ≥1 month prior to mobilization and ≥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: 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 on the ability to drive or use machines 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. For a list of common ADRs and other important safety information associated with mobilisation and apheresis, consult the product SmPC. Very common (≥1/10) ADRs attributed to myeloablative conditioning: Veno-occlusive liver disease, 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 (≥1/100 and <1/10) ADRs attributed to myeloablative conditioning: For a list of other common ADRs and other important safety information associated with myeloablative conditioning, consult the product SmPC. Very common (≥1/10) ADRs attributed to Zynteglo: abdominal pain. Common (≥1/100 and <1/10) ADRs associated with Zynteglo: thrombocytopenia, leukopenia, neutropenia, hot flush, dyspnoea, pain in extremity, non-cardiac chest pain.

Legal Category: Prescription Only Medicine

Marketing Authorisation Number: EU/1/19/1367/001. **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: 28 April 2020 **Reference:** ZYN-EU-00013 v2.0

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of your local full prescribing information on how to report adverse reactions. Please report adverse reactions also to bluebird bio at safety.reporting@bluebirdbio.com.

For medical enquiries, please contact bluebird bio via email at medinfo@bluebirdbio.com.

REFERENCE

1. ZYNTEGLO EU Summary of Product Characteristics. bluebird bio; April 2020

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zynteglo™
(betibeglogene autotemcel)

TREATMENT WITH ZYNTEGLO▼

ZYNTEGLO (betibeglogene autotemcel) is the first and only one-time gene therapy for transfusion-dependent β-thalassaemia (TDT) that gives patients the potential to achieve transfusion independence[1†]

†In clinical trials, transfusion independence was defined as a weighted average haemoglobin of ≥9 g/dL with no red blood cell transfusions for a continuous period of ≥12 months at any time during the study after infusion of ZYNTEGLO.[1]

Please consult the full EU Summary of Product Characteristics (SmPC) before prescribing ZYNTEGLO.

INDICATION

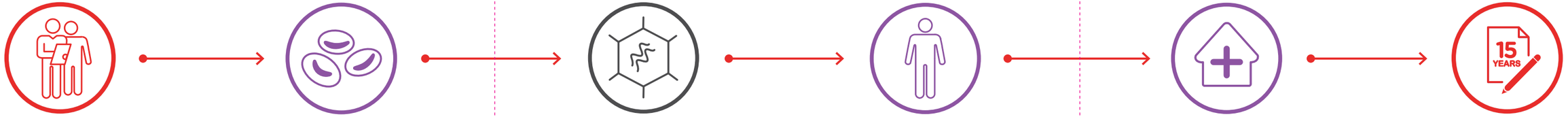
ZYNTEGLO is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)–matched related HSC donor is not available.[1]

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Before prescribing ZYNTEGLO, please refer to the EU Summary of Product Characteristics, which can be found at https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo

zynteglo™
(betibeglogene autotemcel)

Treatment with ZYNTEGLO is managed through a highly coordinated process

By using a patient's own cells, ZYNTEGLO gives patients the potential to achieve transfusion independence without the need for a donor.[1]



CONSULTATION

- Haematologist or other referring physician identifies a potential and appropriate patient for treatment with ZYNTEGLO
- After contacting a Qualified Treatment Centre, the referring physician will schedule a consultation and, if appropriate, schedule an intake time for the patient

COLLECTION[1]

(**Approximately 2 months** prior to ZYNTEGLO infusion)

- Cell collection is required for treatment, since ZYNTEGLO uses the patient's own haematopoietic stem cells
- Includes mobilisation followed by apheresis
- Mobilisation and apheresis may be repeated to ensure collection of sufficient stem cells for treatment

MANUFACTURING[1]

- Collected patient cells are shipped to licensed manufacturing facilities and genetically modified with copies of the $\beta^{A\text{-}T87Q}$-Globin-globin gene in order to manufacture ZYNTEGLO
- ZYNTEGLO is then cryopreserved and stored until ready to be shipped to a ZYNTEGLO Qualified Treatment Centre

CONDITIONING[1]

(At least **6 days** before ZYNTEGLO infusion). In clinical trials, a 4-day regimen of busulfan was the only myeloablative conditioning tested with ZYNTEGLO

- Full myeloablative conditioning (a chemotherapy given over 4 days) must be administered before infusion of ZYNTEGLO

INFUSION AND MONITORING[1]

(Approximately **3 to 6 weeks** in the hospital setting)

- ZYNTEGLO is administered to the patient via intravenous infusion at a Qualified Treatment Centre
- Per clinical judgement, patients will remain in hospital until they are ready to be discharged

REGISTRY[1]

(For **15 years** following administration of ZYNTEGLO)

- The possibility of enrolling in the product registry for up to 15 years should be discussed with patients receiving ZYNTEGLO
- The registry collects data on safety and efficacy of treatment
- NOTE: Restarting iron chelation after ZYNTEGLO infusion may be necessary and should be based on clinical practice; phlebotomy can be used in lieu of iron chelation, when appropriate

PATHWAY KEY

- These steps take place outside of a Qualified Treatment Centre.
- These steps take place at a Qualified Treatment Centre.
- This step takes place at a licensed manufacturing facility.