Plerixafor use in patients with transfusion-dependent beta-thalassaemia who are eligible for treatment with exagamglogene autotemcel (Ages 12 years and above) [URN: 2346]

NHS England commissioning statement

Publication date: 19 August 2024

Commissioning position

1. This commissioning statement aims to standardise the criteria for plerixafor use for stem cell mobilisation in patients with transfusion dependent beta-thalassaemia (TDT) who are eligible to receive treatment with exagamglogene autotemcel to optimise the use of limited resources and ensure equitable access for patients across England.
2. This commissioning statement supports the delivery of the Final Draft Guidance (FDG) for exagamglogene autotemcel use in patients with TDT and should be used in line with the existing Specialist-Haemoglobinopathy-Teams-Service-Specification.pdf (england.nhs.uk). which sets out standards for commissioned providers.

Information considered

3. Beta-thalassaemia is an inherited (genetic) condition that affects the blood and in particular, the beta globin gene. Some patients with the most severe types of beta-thalassaemia (patients with beta-thalassaemia major and some patients with beta-thalassaemia intermedia) require regular blood transfusions.
4. The National Haemoglobinopathy Registry (NHR) reports that in 2020/21 approximately 1000 people were registered with beta-thalassaemia major and approximately 260 people were registered with beta-thalassaemia intermedia (NHR 2021). TDT is a complex multi-system disease. Iron overload can occur as a result of repeat blood transfusions and can cause tissue damage and impaired function of affected organs, including the heart. Other organs such as the liver and endocrine glands can also be affected, leading to the development of additional, complex health problems.
5. Exagamglogene autotemcel is an autologous ex-vivo gene therapy medicinal product (GTMP). This is a type of cell therapy which is given to an individual as a one-off dose using haematopoietic stem cell transplantation (HSCT). Exagamglogene autotemcel is licensed for the treatment of transfusion-dependent β-thalassemia in patients 12 years of age and older for whom HSCT is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.
6. Exagamglogene autotemcel is made from the patient's own blood stem cells and is made specifically for the individual patient. Blood stem cells can turn into other blood cells, including red cells, white cells and platelets. Cells are taken from the patient, which are then modified using exagamglogene autotemcel and given back to the patient as a cell-based transplant in

hospital. As the patient's own blood stem cells are used in the transplant, this process is referred to as autologous HSCT. For autologous HSCT an HLA-matched, related donor is not required.

7. Prior to receiving treatment with exagamglogene autotemcel, patients with transfusion-dependent beta-thalassaemia are required to undergo mobilisation of their blood stem cells. This is to ensure that a sufficient quantity of their own blood stem cells can be harvested and treated with exagamglogene autotemcel. Mobilisation of stem cells can be achieved using a medicine called granulocyte colony stimulating factor (GCSF), in combination with another medicine called plerixafor.
8. The addition of plerixafor to the mobilisation regimen in patients with transfusion-dependent beta-thalassaemia increases the effectiveness of this process prior to treatment with exagamglogene autotemcel. Plerixafor is given by injection under the skin (subcutaneous injection) and works by mobilising patients own blood stem cells from the bone marrow into the blood stream. Patients can then undergo a procedure to have their blood stem cells harvested (apheresis). The patient's stem cells can then be treated with exagamglogene autotemcel. The use of GCSF and plerixafor as outlined in this commissioning statement is off label.
9. Once a patient's blood stem cells have been harvested, they are sent away for treatment with exagamglogene autotemcel. This treatment works by increasing the production of a special type of haemoglobin within the patient's red blood cells called foetal haemoglobin. Having larger amounts of foetal haemoglobin increases the oxygen-carrying capacity of the patient's red blood cells and improves their function. For patients with transfusion-dependent beta thalassaemia this prevents the need for regular blood transfusions. It can take approximately 6 months from the time the patient's blood cells are collected, for the cells to be treated with exagamglogene autotemcel and returned to the site of patient administration.
10. Once the treated cells have been returned, patients receive a conditioning medicine in hospital, a few days before the planned stem cell transplant. Patients remain in hospital to receive the transplant of their treated stem cells, which are delivered via an infusion. The patient will then remain in hospital until after the infusion.
11. This NHS England Commissioning Statement commissions the use of plerixafor for stem cell mobilisation in patients with transfusion-dependent beta-thalassaemia who are eligible to receive treatment with exagamglogene autotemcel.

Commissioned use

12. In order for a patient with transfusion-dependent beta-thalassaemia to receive treatment with plerixafor, all requirements set out in Annex A must be met. Service providers need to ensure they can fully support this patient group as defined by NICE, including pre- and post-autologous HSCT care and management of plerixafor-related reactions and transplant rejection. Service providers need to ensure robust management of plerixafor is in place, including the appropriate level of pharmacy supervision, correct storage equipment and audit of plerixafor use.

Equality statement

13. Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

    - Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Links to policies and commissioning statements

14. This policy relates to the following guidance, practices and specification:

- National Institute for Health and Care Excellence (NICE)
    - Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]
- NHS England
    - Plerixafor for stem cell mobilisation in adults and children 200601P

Definitions

Apheresis	The process of withdrawing blood from a donor's body and separating the blood out into different types of cells.
Conditioning	This is a course of treatment that prepares the patient for the transplantation of stem cells. Conditioning usually involves a regimen of high dose chemotherapy and aims to destroy the patient's bone marrow, suppress the immune system and make way for the new stem cells.
HLA matched	Human leukocyte antigen (HLA) typing is a genetic test used to match patients and donors for bone marrow, cord blood or organ transplants.
Mobilisation cycle	Stem cell mobilisation is the process of stimulating stem cells from the bone marrow into the bloodstream so that they can be collected for later reinfusion. One mobilisation cycle is defined as mobilisation plus the completion of all collective attempts at apheresis that may occur in each time period.

References

1. Locatelli, F. et al. (2024) ‘Exagamglogene Autotemcel for transfusion-dependent β-thalassemia’, New England Journal of Medicine, 390(18), pp. 1663–1676. doi:10.1056/nejmoa2309673.

2. The National Haemoglobinopathy Register (2021) Annual data report 2020/21 https://nhr.mdsas.com/wp-content/uploads/2022/03/NHR_DataReport2021.pdf. Accessed November 2022.

3. Yannaki, E. *et al.* (2013) ‘Hematopoietic stem cell mobilization for gene therapy: Superior mobilization by the combination of granulocyte–colony stimulating factor plus plerixafor in patients with β-thalassemia major’, *Human Gene Therapy*, 24(10), pp. 852–860. doi:10.1089/hum.2013.163.

Annex A

Starting arrangements for all patients

1. The guidance for treatment with exagamglogene autotemcel for patients with transfusion-dependent beta thalassaemia is covered by the NICE Technology Appraisal Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia.

Inclusion Criteria

2. Patients with a confirmed diagnosis of transfusion-dependent beta-thalassaemia must meet **all** of the following inclusion criteria to be eligible for treatment with plerixafor. The patient:
    - Must meet all of the conditions for treatment with exagamglogene autotemcel as outlined in the NICE Technology Appraisal Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia
    - Must be managed at a recognised centre commissioned to provide treatment with exagamglogene autotemcel
    - Consent, patient evaluation and investigations prior to the commencement of the mobilisation procedure must either be carried out at a recognised centre commissioned to provide treatment with exagamglogene autotemcel, or delegated to an appropriate local hospital, in accordance with the relevant transplant centre policy.

Exclusion Criteria

3. Patients who meet **any** of the following exclusion criteria are contraindicated from treatment with plerixafor:
    - Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC
    - Plerixafor should not be used in pregnant patients. Women of childbearing potential must use effective contraception during treatment with plerixafor.

Plerixafor should be otherwise used in accordance with the SmPC including special warnings and precautions for use.

Starting Criteria

4. The targeted CD34+ collection is ≥15 x10^6 cells/kg at mobilisation required for manufacturing of exagamglogene autotemcel in order to achieve a minimum target dose of 3x10^6 CD34+ cells/kg.
5. One mobilisation cycle is defined as mobilisation plus the completion of all collective attempts at apheresis that may occur from Day 5 to Day 7 (inclusive). Therefore, one mobilisation cycle can include up to a maximum of 3 doses of plerixafor. If the first mobilisation cycle is unsuccessful, further mobilisation cycles will likely only require a schedule up to and including Day 6 (e.g. a maximum of two doses of plerixafor per subsequent mobilisation cycle), assuming sufficient backup cells have been obtained in previous mobilisation cycles.
    - From Day 1 to Day 4 of mobilisation, patients should receive G-CSF product subcutaneously or intravenously (Dosing regimens are set out in the ‘Dosing’ section of this commissioning statement)
    - On Day 5 (apheresis) a further dose of G-CSF product should be administered, along with the first dose of plerixafor. Plerixafor should be administered via subcutaneous injection, 4-6 hours before the start of planned apheresis. (Dosing regimens are set out in the ‘Dosing’

section of this commissioning statement). Prior to apheresis, a CD34+ count should be taken, and the treating Transplant Consultant will determine if this is sufficient to proceed.

- On Day 6 these patients should be given one further dose of subcutaneous plerixafor and one further dose of G-CSF product. An attempt at harvesting should be made 4-6 hours following the second dose of plerixafor if the repeat CD34+ is sufficient.
- On Day 7 of apheresis, if further cell harvest for backup cells is required, a further dose of plerixafor alone (without G-CSF) should be administered. 2×10^6 CD34+ cells/kg are required as backup for rescue therapy in the event of a non-neutrophil engraftment with exagamglogene autotemcel. No collection of cells for manufacturing should occur on that day. The administration of a 3rd dose of plerixafor for the collection of backup cells is generally only required as part of the 1st mobilisation cycle.
- **For patients who require more than one mobilisation and apheresis cycle:**
    - For these patients, further treatment, including the number of mobilisation and apheresis cycles required, should be discussed and agreed at the National Haemoglobinopathy Panel Cellular Therapy Group. Based on limited trial evidence, this is likely to be limited to an extremely small number of patients.
    - Subsequent mobilisation cycles will likely only require a schedule up to and including Day 6 (e.g. a maximum of two doses of plerixafor per subsequent mobilisation cycle), assuming sufficient backup cells have been obtained in the 1st mobilisation cycle.

6. A full blood count and peripheral CD34+ count should be performed prior to harvest. It is the responsibility of the Transplant Consultant, to decide whether the harvest should proceed on the basis of the blood CD34+ estimation.
7. All patients with transfusion-dependent beta thalassaemia who are eligible to receive treatment with exagamglogene autotemcel should receive veno-occlusive disease (VOD) prophylaxis[1] from the time of conditioning.

Stopping Criteria

8. A maximum of 3 doses of plerixafor are permitted per mobilisation cycle.

Dosing

9. G-CSF product

- G-CSF product should be administered subcutaneously or intravenously at a dose of 5µg/kg/dose approximately every 12 hours.
- Splenectomised patients should receive a lower dose of G-CSF product of 5µg/kg/dose once daily for 5-6 days to prevent leucocytosis. This dose may be increased to 5µg/kg/dose approximately every 12 hours if there was no significant increase in white blood cell or peripheral blood CD34+ counts, at the discretion of the treating clinician.
- The body weight used in the calculation of dosing should be taken within 5 days before Day 1 of mobilisation.

10. Plerixafor

- Plerixafor should be administered at a dose of 0.24mg/kg by subcutaneous injection 4-6

[1] Suitable prophylaxis may be with ursodeoxycholic acid and/or defibrotide. The choice of agent used is at the direction of the Trust. The use of defibrotide for the prophylactic treatment of VOD is off-label and Trust policy regarding off-label use of medicines should apply.

hours before the start of each apheresis.

- The body weight used in the calculation of dosing should be taken within 5 days before Day 1 of mobilisation.

The use of plerixafor as outlined in this NHS England commissioning statement is off label. Trust Policy regarding off-label use of medicines should apply.

For further information on G-CSF and plerixafor dosing prior to treatment with exagamglogene autotemcel in TDT please see Annex B.

Monitoring

11. Patients should be monitored in a transplant unit and receive supportive care according to standard practices for patients undergoing haematopoietic stem cell transplantation.

Patient Pathway

12. Patients for stem cell harvesting will be referred to the stem cell collection unit by the transplant team with a written prescription detailing the target stem cell dose required as per JACIE and Human Tissue Authority (HTA) recommendations. Either the transplant team or the collection team (depending on local factors) will be responsible for the authorisation and administration of plerixafor for patients requiring this intervention. There will be no change to existing arrangements following approval of this policy.

Effective from

13. The commissioning statement is effective from the date of publication.
14. This commissioning statement will be reviewed in line with any updates to the NICE Technology Appraisal for exagamglogene autotemcel use in patients with TDT, next due on 11 September 2024.

Recommendations for governance and data collection

15. The use of the plerixafor will be subject to the NHS England prior approval (Blueteq) system.
16. The use of plerixafor in the context of this commissioning statement is off label. Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for these assurance processes.
17. Plerixafor for HSCT mobilisation for autologous stem cell transplantation in adults and children under this policy will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of Blood and Marrow Transplantation Services.
18. All providers involved in the provision of plerixafor and the subsequent harvesting of peripheral blood stem cells must fulfil HTA requirements and must meet JACIE accreditation standards. In addition, regular audit should be carried out on the use of plerixafor. Audit criteria will encompass the following:

    - % of total patients undergoing mobilisation who require plerixafor.
    - Number of doses of plerixafor used per patient.
    - Total CD34+ cells mobilised or sufficient Colony Forming Units (CFU) following plerixafor.
    - Number of collection days required to obtain sufficient cells for indicated Peripheral Blood Stem Cell Transplantation (PBSCT).

- Time to neutrophil and platelet engraftment following PBSCT to assess the quality of the stem cell harvested.

Annex B

Full dosing chart

TDT[2],[3]	**Mobilisation**				**Days of Apheresis**		
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7[4]
G-CSF/filgrastim	X	X	X	X	X	X[5]	
Plerixafor					X[6]	X	X[7]

Information in the Full Dosing Chart supplied by Vertex Pharmaceuticals Incorporated, Boston, MA

[2] Frangoul H, et al. *N Engl J Med* 2021;384(3):252-260. (protocol)
[3] Data on file. Vertex Pharmaceuticals Incorporated, Boston, MA
[4] The third day of apheresis is reserved ONLY for collection of backup cells. No collection of cells for manufacturing should occur on that day.
[5] For subjects with an intact spleen, evening dose of G-CSF administered on Day 6 only if apheresis is planned for Day 7
[6] Administered 4-6 hours before planned apheresis