SUMMARY OF PRODUCT CHARACTERISTICS

▼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 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Aucatzyl 410 × 10^6 cells dispersion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Aucatzyl (obecabtagene autoleucel) is a genetically modified autologous T cell immunotherapy containing T cells transduced *ex vivo* using a lentiviral vector expressing an anti-CD19 chimeric antigen receptor (CAR), comprising a murine anti-CD19 single chain variable fragment linked to a 4-1BB co-stimulatory domain and a CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of Aucatzyl contains obecabtagene autoleucel at a target concentration of 10 × 10^6 total viable cells/mL of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR positive viable T cells). The medicinal product is packaged in three or more infusion bags overall containing a cell dispersion for infusion of a target dose of 410 × 10^6 CAR-positive viable T cells suspended in a cryopreservative solution. Each infusion bag contains 10-20 mL or 30-70 mL of dispersion for infusion.

The quantitative information of medicinal product, including the number of infusion bags (see section 6) to be administered, is presented in the Release for Infusion Certificate provided via the Autolus Scheduling Portal and located inside the lid of the vapour phase of a liquid nitrogen shipper used for transporting the medicinal product.

Excipient(s) with known effect

This medicinal product contains 7.5% dimethyl sulfoxide, and up to 1131 mg sodium and 39 mg potassium per total dose (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersion for infusion.

Colourless to pale yellow, very opalescent dispersion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aucatzyl is indicated for the treatment of adult patients (≥ 18 years) with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (see section 5.1).

4.2 Posology and method of administration

Aucatzyl must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Aucatzyl.

Refer to the UK Public Assessment Report on the Medicines and Healthcare products Regulatory Agency (MHRA) website for details of leukapheresis, lymphodepletion and bridging therapies used in the clinical trials for Aucatzyl.

Posology

Aucatzyl is intended for autologous use (see section 4.4).

The target dose of Aucatzyl is 410×10^6 CD19 CAR-positive viable T cells supplied in three or more infusion bags.

See the Release for Infusion Certificate and Dose Schedule Planner for the actual cell counts and volumes to be infused and to guide the appropriate dosage regimen (see section 6.6).

Bone marrow assessment

A bone marrow assessment must be available from a biopsy and/or aspirate sample obtained within 7 days prior to the commencement of the lymphodepleting chemotherapy.

The bone marrow assessment is used to determine the Aucatzyl dosage regimen.

The treatment regimen consists of a split dose to be administered on Day 1 and Day 10 (± 2 days).

Low Tumour Burden Regimen (where lymphoblasts make up ≤ 20% of all nucleated cells in a bone marrow biopsy obtained within 7 days prior to lymphodepletion):

- Day 1: 100×10^6 cells administered via bag infusion
- Day 10 (± 2 days): 10×10^6 cells administered via syringe and 300×10^6 cells administered via bag infusion

High Tumour Burden Regimen (where lymphoblasts make up > 20% of all nucleated cells in a bone marrow biopsy obtained within 7 days prior to lymphodepletion):

- Day 1: 10×10^6 cells administered via syringe
- Day 10 (± 2 days): 100×10^6 cells administered via bag infusion and 300×10^6 cells administered via bag infusion

If bone marrow assessment results are inconclusive:

- Repeat the biopsy or aspirate, and note that a repeat biopsy or aspirate must only be taken prior to lymphodepleting chemotherapy.
- If results remain inconclusive, proceed with High Tumour Burden Regimen (i.e. administration of the 10×10^6 dose on Day 1) per the Aucatzyl Dose Schedule Planner.

Pretreatment conditioning (lymphodepleting chemotherapy)

Confirm availability of Aucatzyl prior to starting lymphodepleting chemotherapy.

Refer to the UK Public Assessment Report on the MHRA website for details of the lymphodepletion therapy used in the FELIX clinical trial for Aucatzyl.

Premedication

- To minimise the risk of an infusion reaction, premedicate with paracetamol (1,000 mg orally) approximately 30 minutes prior to Aucatzyl infusion.
- Avoid prophylactic use of systemic corticosteroids because this may interfere with the activity of Aucatzyl.

Special populations

Elderly

No dose adjustment is required in patients over 65 years of age. Twenty percent of patients treated with Aucatzyl in the safety set (25/127) were 65 years of age and over. Overall, differences in safety and efficacy were not observed between elderly and younger adult patients, see section 5.2.

Renal and hepatic impairment

There is no clinical experience in patients with renal or hepatic impairment. Patients with a history of renal or hepatic impairment are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention, and consideration on a case-by-case basis.

Paediatric population

The safety and efficacy of Aucatzyl in children and adolescents below 18 years of age have not yet been established.

Method of administration

Aucatzyl is for autologous and intravenous use only.

For instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Aucatzyl see section 6.6. Strictly follow Administration Instructions to minimise dosing errors.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Refer to the UK Public Assessment Report on the MHRA website for details of leukapheresis, lymphodepletion and bridging therapies used in the FELIX clinical trial for Aucatzyl.

Traceability

The 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 must be kept for a period of 30 years after the expiry date of the product.

Autologous use

Aucatzyl is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Aucatzyl must not be administered if the information on the product labels and Release for Infusion Certificate do not match the patient's identity.

Monitoring

- Patients must be monitored daily for 14 days after the first infusion for signs and symptoms of cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and other toxicities.
- Frequency of monitoring after the first 14 days may be carried out at the physician's discretion and continued for at least 4 weeks after the first infusion.
- Patients must be instructed to remain within proximity of the qualified treatment centre for at least 4 weeks following the first infusion.

Reasons to delay treatment

Delay Aucatzyl treatment if there are unresolved serious adverse reactions from preceding chemotherapies, if the patient is experiencing severe intercurrent infection, or has active graft-versus-host disease. If the patient requires supplementary oxygen, Aucatzyl should only be infused, if considered appropriate, based on the treating physician's benefit / risk assessment.

Reasons to delay the second split dose

Dosage delays or discontinuation may be required after the first split dose to manage adverse reactions.

Patients with Grade 2 cytokine release syndrome and / or Grade 1 immune effector cell- associated neurotoxicity syndrome following the first split dose may receive the second dose on Day 10 (± 2 days) up to Day 21 only if cytokine release syndrome has resolved to Grade 1 or less and immune effector cell-associated neurotoxicity syndrome has completely resolved.

For patients with Grade ≥ 3 (i) severe infection at the time of infusion of Aucatzyl or (ii) requirement for supplementary oxygen or (iii) other clinically relevant adverse reactions following the first split dose: consider postponing Aucatzyl up to Day 21 to allow the situation to resolve.

In addition, the second split dose is not to be administered if ≥ Grade 3 cytokine release syndrome, ≥ Grade 2 immune effector cell-associated neurotoxicity syndrome and / or ≥ Grade 3 pulmonary or cardiac toxicities are observed following the first split dose.

Grading is based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Cytokine release syndrome

Refer to local institutional / national guidelines for advice on monitoring and management of cytokine release syndrome.

Evaluation for haemophagocytic lymphohistiocytosis / macrophage activation syndrome is to be considered in patients with severe or unresponsive cytokine release syndrome. Treatment should be administered per institutional standards.

Availability of tocilizumab

Treatment centres must have 24-hour immediate access to tocilizumab and emergency equipment must be available prior to infusion. In the exceptional case where tocilizumab is not available owing to a shortage, then alternatives to tocilizumab to treat cytokine release syndrome must be available prior to infusion. Shortages of tocilizumab may be checked for in the MHRA Central Alerting System.

Immune Effector Cell-associated Neurotoxicity Syndrome

Patients should be monitored for signs and symptoms of immune effector cell-associated neurotoxicity syndrome.

Refer to local institutional / national guidelines for advice on monitoring and management of immune effector cell-associated neurotoxicity syndrome.

Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Aucatzyl infusion and should be managed according to institutional guidelines.

Patient blood counts must be monitored after Aucatzyl infusion.

Severe infections

Aucatzyl should not be administered to patients with clinically significant active systemic infections. Severe infections, including life-threatening or fatal infections occurred in patients after receiving Aucatzyl (see section 4.8).

Grade 3 or higher febrile neutropenia was observed in patients after Aucatzyl infusion (see section 4.8) and may be concurrent with cytokine release syndrome.

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection

There is no clinical experience in patients with a positive test for HIV, active HBV, or active HCV infection. Screening for HBV, HCV, HIV and other infectious agents must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Leukapheresis material from patients with active HIV, active HBV, or active HCV infection will not be accepted for manufacturing.

Viral reactivation

Viral reactivation, e.g., HBV reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Hypogammaglobulinaemia

Hypogammaglobulinaemia is caused by B cell aplasia and has been seen as a consequence of depletion of normal B cells by CAR T cell therapy.

Hypogammaglobulinaemia can occur in patients treated with Aucatzyl (see section 4.8).

Hypogammaglobulinaemia predisposes patients to become more susceptible to infections. Immunoglobulin levels should be monitored after treatment with Aucatzyl and managed per institutional guidelines including infection precautions, antibiotics or antiviral prophylaxis and immunoglobulin replacement.

Prior stem cell transplantation (graft versus host disease)

It is recommended that patients do not receive Aucatzyl within 3 months of undergoing an allogeneic stem cell transplantation because of the potential risk of Aucatzyl worsening graft versus host disease. There must be a gap of 3 months after allogeneic stem cell transplantation before leukapheresis is carried out to obtain material to manufacture Aucatzyl.

Stem cell transplantation after CAR T cell therapy

The role of allogeneic stem cell transplant following CAR T cell therapy is unclear. Note: a chemotherapy-based preparative regimen associated with a subsequent stem cell transplant procedure will neutralise the effect of CAR T cells.

Secondary malignancies including of T cell origin

Patients treated with Aucatzyl may develop secondary malignancies. T cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T cell therapy. T cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-directed CAR T cell therapy. There have been fatal outcomes. Patients should be monitored life-long for signs of secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on the collection of patient samples for testing.

Tumour lysis syndrome

Tumour lysis syndrome, which may be severe, has occasionally been observed in the FELIX trial and with other CAR T cell products. To minimise the risk of tumour lysis syndrome, patients with high tumour burden should receive tumour lysis syndrome prophylaxis as per standard guidelines prior to Aucatzyl infusion. Signs and symptoms of tumour lysis syndrome after Aucatzyl infusions must be monitored, and events managed according to standard guidelines.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, may occur due to dimethyl sulfoxide in Aucatzyl.

Transmission of an infectious agent

Although Aucatzyl is tested for Sterility and Mycoplasma, a risk of transmission of infectious agents exists. Healthcare professionals administering Aucatzyl must, therefore, monitor patients for signs and symptoms of infection after treatment and treat appropriately, if needed.

Interference with virological testing

Due to limited and short spans of identical genetic information between the lentiviral vector used to create Aucatzyl and HIV, some HIV nucleic acid tests may give a false positive result.

Blood, organ, tissue and cell donation

Patients treated with Aucatzyl must not donate blood, organs, tissues and cells for transplantation.

Patient Card

The Patient Card must be given to the patient after treatment.

Sodium Content

This medicinal product contains 1131 mg sodium per target dose, equivalent to 57% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Potassium Content

This medicinal product contains 39 mg potassium per target dose, equivalent to 1% of the WHO recommended maximum daily intake of 3.51 g potassium for an adult.

Long-term follow-up

Patients are expected to be enrolled in a long-term follow-up scheme in order to better understand the long-term effects of Aucatzyl.

Paediatric population

There is not any clinical experience of Aucatzyl in paediatric patients. No specific guidance for use in this patient population exists.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Some patients required tocilizumab and/or corticosteroids for the management of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (see section 4.4).

Prophylactic use of systemic corticosteroids may interfere with the activity of Aucatzyl. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section 4.2).

Patients with high tumour burden (≥ 20%) had a greater frequency of cytokine release syndrome, which was managed by the use of tocilizumab and/or corticosteroids. Patients with a higher tumour burden showed a more robust CAR T cell expansion which is known to increase the likelihood of occurrence of cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. Administration of tocilizumab or corticosteroids for the treatment of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome did not affect the rate or extent of expansion and persistency.

Live vaccines

The safety of immunisation with live viral vaccines during or following treatment with Aucatzyl has not been studied. As a precautionary measure, vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepletion chemotherapy, during Aucatzyl treatment, and until immune recovery following treatment. Refer to local institutional / national guidance for advice on live vaccines.

Bridging Therapies

Blinatumomab was not permitted as a bridging therapy in the FELIX clinical study, and there is no clinical experience with use of this product as a bridging therapy before Aucatzyl treatment.

Herbal remedies with immunomodulatory properties

There are no formal interaction studies with herbal remedies and Aucatzyl; general precautions are recommended due to their potential immunomodulatory effects.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

The pregnancy status of women of childbearing potential must be verified before starting Aucatzyl treatment.

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There is insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Aucatzyl.

For females who are not postmenopausal (< 24 months of amenorrhea) or who are not surgically sterile (absence of ovaries and/or uterus), two methods of contraception, comprising of one highly effective method of contraception together with a barrier method, must be used during the treatment period and for at least 12 months after the last dose of Aucatzyl. They must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during treatment and for 12 months after receiving the last dose of Aucatzyl.

Pregnancy

There are limited data available with the use of Aucatzyl in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Aucatzyl to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if Aucatzyl has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B cell lymphocytopenia. Therefore, Aucatzyl is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women must be advised on the potential risks to the foetus.

Pregnancy after Aucatzyl therapy must be discussed with the treating physician.

Assessment of immunoglobulin levels and B cells in newborn infants of mothers treated with Aucatzyl must be considered.

Breast-feeding

It is unknown whether Aucatzyl cells are excreted in human milk or transferred to the breast-feeding child. Breast-feeding women must be advised of the potential risk to the breast-fed child.

Fertility

There are very limited data on the effect of Aucatzyl on fertility. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Aucatzyl may have a major influence on the ability to drive and use machines.

Because of the potential for neurological events, including altered mental status or seizures, patients must refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of the neurological event as confirmed by the treating physician.

4.8 Undesirable effects

Summary of the safety profile

The safety of Aucatzyl was evaluated in one open-label, single-arm study (study FELIX) in which 127 adult patients with relapsed or refractory B cell acute lymphoblastic leukaemia received a median dose of 410×10^6 viable CAR T cells (range: 10 to 480×10^6 viable CAR T cells).

Exposure to Aucatzyl was preceded by unstimulated leukapheresis followed by lymphodepletion with fludarabine and cyclophosphamide (safety profiles for these procedures were generally consistent with those expected with leukapheresis and lymphodepletion). Bridging therapy was permitted.

The median (minimum, maximum) duration of follow-up after being administered Aucatzyl is 21.5 (8.6, 41.4) months.

The most common adverse reaction of any grade included cytokine release syndrome (69%), infections-pathogen unspecified (45%) and musculoskeletal pain (31%).

The most common non-laboratory Grade 3 or higher adverse reactions were infections-pathogen unspecified (32%), febrile neutropenia (24%) and bacterial infectious disorders (11%).

The most common serious adverse reactions of any grade included infections-pathogen unspecified (28%), febrile neutropenia (13%) and immune effector cell-associated neurotoxicity syndrome (9%).

Patients undergo leukapheresis, bridging therapy and lymphodepletion therapy prior to administration of Aucatzyl. Refer to local / national guidance documents for information on adverse events that may occur in association with the leukapheresis procedure. Refer to the relevant summaries of product characteristics for information on adverse events that may arise subsequent to exposure to medicinal products used in the bridging and lymphodepletion therapies.

Tabulated list of adverse reactions

Table 1 summarises the adverse reactions in a total of 127 patients exposed to Aucatzyl in the Phase Ib and Phase II FELIX study. These reactions are presented by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions identified with Aucatzyl

System Organ Class (SOC)	**Frequency**	**Adverse reaction**
Infections and infestations		
	Very Common	Infections – pathogen unspecified Bacterial infectious disorders COVID-19 Viral infectious disorders excluding COVID-19 Fungal infectious disorders
Blood and lymphatic system disorders		
	Very Common	Neutropenia[a] Leukopenia[a] Lymphopenia[a] Thrombocytopenia [a] Anaemia[a] Febrile neutropenia Coagulopathy
Immune system disorders		

	Very Common	Cytokine release syndrome
	Common	Hypogammaglobulinaemia Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders		
	Very Common	Decreased appetite
Psychiatric disorders		
	Common	Delirium
Nervous system disorders		
	Very Common	Headache Immune effector cell-associated neurotoxicity syndrome Encephalopathy Dizziness
	Common	Tremor
Cardiac disorders		
	Very Common	Tachycardia
	Common	Arrhythmia Cardiac Failure Palpitations
Vascular disorders		
	Very Common	Hypotension Haemorrhage
Respiratory, thoracic and mediastinal disorders		
	Very Common	Cough
Gastrointestinal disorders		
	Very Common	Nausea Diarrhoea Vomiting Abdominal Pain Constipation
	Common	Stomatitis
Skin and subcutaneous tissue disorders		
	Very Common	Rash
Musculoskeletal and connective tissue disorders		
	Very Common	Musculoskeletal pain
General disorders and administration site conditions		
	Very Common	Pyrexia Pain Fatigue Oedema
	Common	Chills

Investigations		
	Very Common	Alanine aminotransferase increased[a] Weight decreased Hyperferritinaemia Aspartate aminotransferase increased[a]
Injury, poisoning and procedural complications		
	Common	Infusion related reaction
[a] Frequency based on Grade 3 or higher laboratory parameter.		

Description of selected adverse reactions

Cytokine release syndrome

Cytokine release syndrome was reported in 69% (87/127) of patients, including Grade 3 cytokine release syndrome in 2% (3/127) of patients. There were no reported Grade 4 or 5 events. The median time to onset of cytokine release syndrome of any grade was 8 days (range: 1 to 23 days) with a median duration 5 days (range: 1 to 21 days). The most common manifestations of cytokine release syndrome among patients who experienced cytokine release syndrome included fever (69%), hypotension (25%) and hypoxia (13%).

Sixty-four percent (56/87) of patients experienced cytokine release syndrome after the first, but prior to the second infusion of Aucatzyl. In the study, 80% (70/87) of patients who experienced cytokine release syndrome had a high tumour burden at the time of lymphodepleting treatment (≥ 5% lymphoblasts in the bone marrow), with 39% (34/87) of patients presenting with > 75% lymphoblast in their bone marrow. The primary treatment for cytokine release syndrome was tocilizumab (76%; 66/87), with patients also receiving corticosteroids (23%; 20/87) and other anti cytokine therapies (14%; 12/87).

Haemophagocytic Lymphohistiocytosis / Macrophage Activation Syndrome

Haemophagocytic lymphohistiocytosis / macrophage activation syndrome, including severe and life threatening reactions may occur following treatment with Aucatzyl. Haemophagocytic lymphohistiocytosis / macrophage activation syndrome was reported in 2% (2/127) of patients and included Grade 3 and Grade 4 events with a time of onset at Day 22 and Day 41, respectively. One patient experienced a concurrent immune effector cell-associated neurotoxicity syndrome event after Aucatzyl infusion.

Immune Effector Cell-Associated Neurotoxicity Syndrome

Immune effector cell-associated neurotoxicity syndrome, which may be severe, life-threatening or fatal, occurred in 23% (29/127) of patients, including Grade ≥ 3 in 7% (9/127) of patients following treatment with Aucatzyl.

In clinical studies, 90% (26/29) of patients who experienced immune effector cell-associated neurotoxicity syndrome and all patients who experienced Grade ≥ 3 immune effector cell-associated neurotoxicity syndrome had > 5% lymphoblasts in their bone marrow at the time of lymphodepleting treatment. Among the 9 patients who experienced Grade ≥ 3 immune effector cell-associated neurotoxicity syndrome, 56% (5/9) of patients presented with > 75% lymphoblasts in their bone marrow. Among the 29 patients who experienced immune effector cell-associated neurotoxicity syndrome, 62% (18/29) experienced an onset after the second infusion of Aucatzyl.

The median time to onset for immune effector cell-associated neurotoxicity syndrome events was 12 days (range: 1 to 31 days) with a median duration of 8 days (range: 1 to 53 days). The most common symptoms included (> 2%) confusional state (9.4%) and tremor (4.7%).

Eighty-three percent (24/29) of patients received treatment for immune effector cell-associated neurotoxicity syndrome. All treated patients received high-dose corticosteroids and 50% (12/24) of patients received anti-epileptics prophylactically.

Prolonged Cytopenia

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Aucatzyl infusion.

In patients who were responders to Aucatzyl, Grade ≥ 3 cytopenias at Month 1 following infusion were observed in 69% (68/99) of patients and included neutropenia (59%, 58/99) and thrombocytopenia (49%, 48/99). Grade 3 or higher cytopenias at Month 3 following Aucatzyl infusion was observed in 20% (20/99) of patients and included neutropenia (13%, 13/99) and thrombocytopenia (11%, 11/99).

Severe Infections

Severe, life-threatening and fatal infections occurred in patients after Aucatzyl infusion. Non-COVID-19 infections of all grades occurred in 71% (90/127) of patients. Grade 3 or higher non-COVID-19 infections were reported in 45% (57/127) of patients.

Grade 3 or higher febrile neutropenia was observed in 24% (30/127) of patients after Aucatzyl infusion and may be concurrent with cytokine release syndrome.

Monitor patients for signs and symptoms of infection before and after Aucatzyl infusion and treat appropriately (see section 4.4). Administer prophylactic antimicrobials according to local guidelines.

Hypogammaglobulinaemia

Hypogammaglobulinaemia was reported in 9% (12/127) of patients treated with Aucatzyl including 2 cases (2%, 2/127) of Grade 3 hypogammaglobulinaemia.

Immunogenicity

The humoral immunogenicity of Aucatzyl was measured using an assay for the detection of anti-drug antibodies against Aucatzyl. In the FELIX study, 8.7% (11/127) of patients tested positive for anti-CD19 CAR antibodies pre-infusion. Treatment induced anti-CD19 CAR antibodies were detected in 1.7% (2/127) of patients. There is no evidence that the presence of pre-existing or post-infusion anti-CD19 CAR antibodies impact the effectiveness, safety, initial expansion and persistency of Aucatzyl.

The cellular immunogenicity of Aucatzyl was measured using an assay for the detection of T cell responses, measured by production of interferon gamma (IFNγ), to the full length anti-CD19 CAR. Only 4% (3/75) of patients tested positive in the cellular immunogenicity readout (IFNγ) post-infusion. There is no evidence that the cellular immunogenicity impacts the kinetics of initial expansion and persistence of Aucatzyl, or the safety or effectiveness of Aucatzyl.

Secondary malignancies

There have been cases of the following adverse effect(s) reported after treatment with other CAR T cell products, which might also occur after treatment with Aucatzyl: secondary malignancy of T cell origin.

Paediatric population

Clinical safety in a paediatric population has not yet been evaluated.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

During clinical studies, occurrences of overdose were observed at the administration of the first dose in 4% (5/127) of patients. All 5 patients had high tumour burden and should have received a 10×10^6 first dose but received a higher dose between 68 and 103×10^6 CAR T cells. Cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and haemophagocytic lymphohistiocytosis, including severe events, were observed in patients who experienced overdose. In the event of a suspected overdose, any adverse reactions are to be treated in accordance with guidance provided in section 4.4.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic cell and gene therapy, ATC code: L01XL12.

Mechanism of action

Aucatzyl is a CD19-directed genetically modified autologous T cell immunotherapy consisting of the patient's own T cells expressing an anti-CD19 (CAT) CAR. Engagement of anti-CD19 (CAT) CAR positive T cells with CD19 expressed on target cells, such as cancer cells and normal B cells, leads to activation of the anti-CD19 (CAT) CAR-positive T cells and downstream signalling through the CD3-zeta domain. Proliferation and persistence by the anti-CD19 (CAT) CAR-positive T cells following activation are enhanced by the presence of the 4-1BB co-stimulatory domain. This binding to CD19 results in anti-tumour activity and killing of CD19-expressing target cells.

Pharmacodynamic effects

Serum concentrations of cytokines such as IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factors were evaluated pre- and up to 3 months post Aucatzyl infusion. Peak elevation of plasma cytokines was observed by Day 28 after Aucatzyl infusion and concentrations returned to baseline by Month 3.

Due to the on-target effect of Aucatzyl, a period of B cell aplasia is expected.

Clinical efficacy and safety

The efficacy and safety of Aucatzyl is based on the results of the FELIX study, an open-label, multi-centre, single-arm study of Aucatzyl in adult patients with relapsed or refractory B cell acute lymphoblastic leukaemia. The study is on-going.

Patients in the pivotal study were adults (≥ 18 years) with relapsed or refractory CD19-positive B cell acute lymphoblastic leukaemia, who experienced one of the following: first relapse following a remission lasting ≤ 12 months, relapsed or refractory B cell acute lymphoblastic leukaemia after two or more prior lines of systemic therapy, or relapsed or refractory B cell acute lymphoblastic leukaemia at least greater than 3 months after allogeneic stem cell transplantation.

The study excluded patients with active or serious infections requiring systemic antimicrobials for management, active graft versus host disease, and history or presence of clinically relevant disorders of the central nervous system (CNS). Also patients with CNS-2 disease (lymphoblasts with less than 5 total white blood cells per mL in a cerebrospinal fluid sample) with neurologic changes and CNS-3 disease (lymphoblasts with more than or equal to 5 total white blood cells per mL in a cerebrospinal fluid sample or the sample is grossly traumatic) irrespective of neurological changes were also excluded. Therefore, data are limited in patients with CNS-2 disease with neurologic changes or CNS-3 disease, and the benefit/risk of Aucatzyl has not been established in these patients.

Refer to the UK Public Assessment Report on the MHRA website for a more complete description of the design, conduct, analysis and outcomes of the FELIX study (includes information on leukapheresis, bridging therapies and lymphodepletion therapies used in the FELIX study.

One hundred and twelve (112) adult patients with relapsed / refractory acute lymphoblastic leukaemia were enrolled into Cohort IIA, the main analysis cohort of study FELIX. Patients in cohort IIA had ≥ 5% lymphoblasts in the bone marrow at screening.

Eighteen (18) patients discontinued the study without receiving an Aucatzyl infusion – 11 patients died before infusion, 5 did not receive the drug due to manufacturing issues, 1 patient had an adverse event, and 1 patient discontinued due to physician’s decision.

Ninety four (94) patients were administered at least one infusion of Aucatzyl.

Infused patients had received between 1 and 6 prior therapies with a median of 2; 12 patients had disease that was refractory to all previous therapies; 36 patients had received a stem cell transplant; 48 patients had received blinatumomab or inotuzumab ozogamicin; and 25 patients returned a positive result for the Philadelphia chromosome.

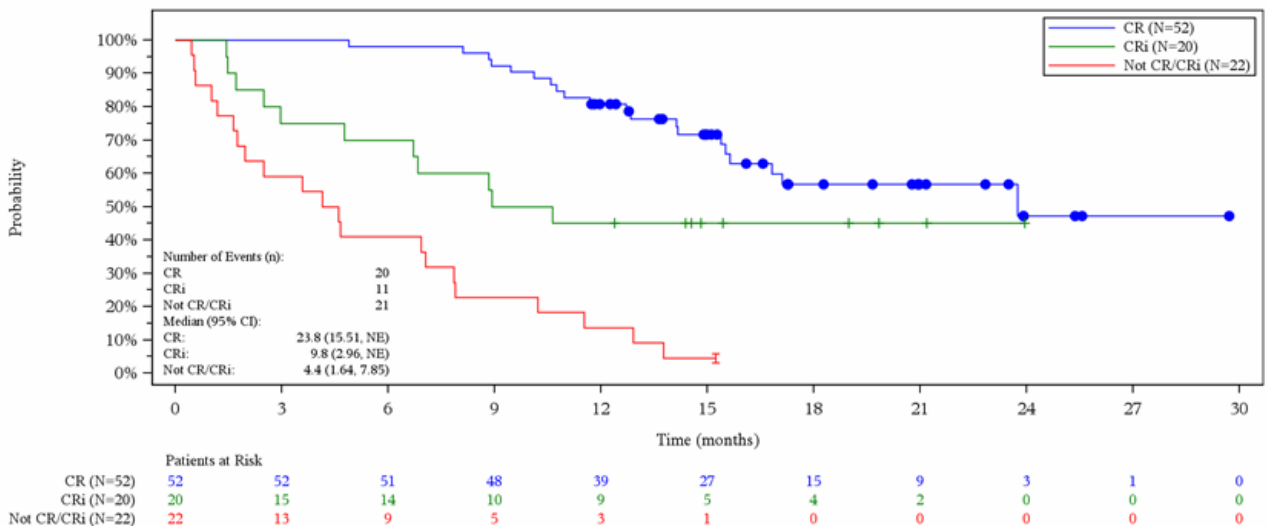
Prior to lymphodepletion: 19 had extramedullary disease; 30 had > 75% lymphoblasts in bone marrow; 27 had > 20 to 75% bone marrow lymphoblasts; and 37 had up to 20% bone marrow lymphoblasts.

The median time from leukapheresis to product release was 20 days (range: 17 to 43) and the median time from leukapheresis to Aucatzyl infusion was 36 days (range: 25 to 92).

For the 94 patients in the infused set, the median dose received was 410 × 10^6 CD19 CAR-positive viable T cells (range: 10 to 480 × 10^6). Eighty five (85) patients (90.4%) received the total target dose of 410 × 10^6 CD19 CAR-positive viable T cells. Six (6) patients (6.4%) received the first dose only, primarily due to adverse events (3.2%), progressive disease (1.1%), manufacturing related issues (1.1%), and death (1.1%). Three (3) patients received a dose different to the target dose.

Overall survival is summarised in the following figure and table.

Figure 1: Kaplan-Meier Plot of Overall Survival Without Censoring SCT as Assessed by IRRC (Cohort IIA, Infused Set)



Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; IRRC = Independent Response Review Committee; NE = not estimable; SCT = stem cell transplantation.

Median with 95% CIs are calculated from PROC LIFETEST output method (Brookmeyer and Crowley 1982).

Cut off date: 07-Feb-2024.

Table 2: Overall Survival Without Censoring SCT By Best Overall Response with Disease Assessment by IRRC (Cohort IIA, Infused Set)

	CR (N=52) n (%)	CRi (N=20) n (%)	Not CR/CRi (N=22) n (%)	Total (N=94) n (%)
No. of patients in analysis[1]	52	20	22	94
No. of events - n (%)	20 (38.5)	11 (55.0)	21 (95.5)	52 (55.3)
Death	20 (38.5)	11 (55.0)	21 (95.5)	52 (55.3)
No. of censored	32 (61.5)	9 (45.0)	1 (4.5)	42 (44.7)

observations - n (%)				
Alive	32 (61.5)	9 (45.0)	1 (4.5)	42 (44.7)
Quartile Estimates (95% CI) [month][2]				
50th	23.75 (15.51, NE)	9.79 (2.96, NE)	4.37 (1.64, 7.85)	14.16 (10.97, 23.75)
Event-free probability estimate (95% CI)[3]				
6 months	98.1 (87.1, 99.7)	70.0 (45.1, 85.3)	40.9 (20.9, 60.1)	78.7 (69.0, 85.7)
12 months	80.8 (67.2, 89.2)	45.0 (23.1, 64.7)	13.6 (3.4, 30.9)	57.4 (46.8, 66.7)
18 months	56.7 (40.0, 70.4)	45.0 (23.1, 64.7)	NE	41.1 (30.0, 51.8)

Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; IRRC = Independent Response Review Committee; NE = not estimable; SCT = stem cell transplantation.

[1] The analysis includes all patients in the Infused Set – Cohort IIA.

[2] Percentiles with 95% CIs are calculated from PROC LIFETEST output method (Brookmeyer and Crowley 1982).

[3] % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates, with 95% CIs estimated using Greenwood formula.

Cut off date: 07-Feb-2024.

Paediatric population

The MHRA has deferred the obligation to submit the results of studies with Aucatzyl in one or more subsets of the paediatric population with B cell acute lymphoblastic leukaemia and has waived the obligation to submit the results of studies with Aucatzyl for the treatment of acute lymphoblastic leukaemia in the paediatric population weighing less than 6 kg, see section 4.2 for information on paediatric use.

Conditional Approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme.

This means that further evidence on this medicinal product is awaited. The Medicines and Healthcare products Regulatory Agency will review new information on this medicinal product at least every year and this Summary of Product Characteristics will be updated as necessary.

5.2 Pharmacokinetic properties

Cellular kinetics

Studies demonstrate Aucatzyl has a distinct mode of action with a fast off-rate of $3.1 \times 10^{-3} s^{-1}$ of its CD19 binding domain. The short interaction between Aucatzyl with CD19-positive target cells mimics physiological T cell activation and may result in reduced cytokine release and immunotoxicity while preserving robust CAR T expansion and persistency.

The pharmacokinetics of Aucatzyl were assessed in the 94 patients with relapsed or refractory CD19-positive B cell acute lymphoblastic leukaemia receiving a median dose of 410×10^6 CD19 CAR-positive viable T cells (range: 10 to 480×10^6 CD19 CAR-positive viable T cells) in Cohort IIA.

Following Day 1 infusion, levels of Aucatzyl transgene in peripheral blood exhibited an initial rapid and robust expansion. The median time of maximal expansion to peak (t_{max}) occurred at Day 14 (range: Day 2 to 55), demonstrated by a peak CAR T concentration (C_{max}) of 114,982 copies/µg genomic DNA (gDNA; range: 129 to 600,000) and a geometric mean area under the curve between Days 0 and 28 (AUC_{0-28d}) of 1,138,188 day*copies/µg DNA (range 17,900 to 7,230,000 day*copies/µg DNA).

A high level of expansion was generally observed regardless of response status (CR/CRi vs. non-CR/non-CRi). Furthermore, 81% (21/26) of patients who had ongoing remission had ongoing CAR T persistency at the last laboratory assessment, with a maximum observed persistency of 27.7 months.

Patients who received a first split dose of 10×10^6 cells (> 20% lymphoblast) demonstrated a higher expansion of CAR T cells (C_{max} and AUC_{0-28d}) compared to patients who received a first split dose of 100×10^6 cells (≤ 20% lymphoblast). In turn, patients with high expansion tended to have higher rates of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Therefore, high tumour burden is the main risk factor for onset of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.

Administration of tocilizumab or corticosteroids for the treatment of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome did not impact the rate or extent of expansion and persistency. Persistency was not impacted by tumour burden.

Of the 94 patients in the infused set (Cohort IIA), 9 patients experienced a permitted delay to infusion of the second dose to resolve their cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. Despite low numbers, no indication of decreased persistency or efficacy was observed in patients receiving a delayed second dose.

<u>Specific populations</u>

Gender or age did not have a significant impact on the pharmacokinetics of Aucatzyl (C_{max}, $AUC_{0\text{-}28d}$ or persistency).

Hepatic and renal impairment studies of Aucatzyl were not conducted.

5.3 Preclinical safety data

Aucatzyl comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

No carcinogenicity, mutagenicity or genotoxicity studies have been conducted with Aucatzyl.

No studies have been conducted to evaluate the effects of Aucatzyl on fertility, reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Dimethyl sulfoxide

Human albumin solution

Phosphate buffered saline: potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate, water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Frozen: 6 months at ≤ -150 °C.

Once thawed: 1 hour at room temperature.

6.4 Special precautions for storage

Aucatzyl must be stored in the vapour phase of liquid nitrogen (≤ -150 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Thawed medicinal product should not be refrozen.

For storage conditions and duration after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ethylene vinyl acetate infusion bag(s) with a sealed filling tube and two available spike ports, containing either 10-20 mL (50 mL bags) or 30-70 mL (250 mL bags) cell dispersion. One individual treatment regimen includes 3 or more infusion bags for the total target dose of 410×10^6 CD19 CAR-positive viable T cells. Each infusion bag is individually packed within an overwrap in a metal cassette.

6.6 Special precautions for disposal

Irradiation could lead to inactivation of the product.

Precautions to be taken before handling or administering the medicinal product

Aucatzyl must be transported within the treatment centre in closed, break-proof, leak-proof containers.

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Aucatzyl must take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

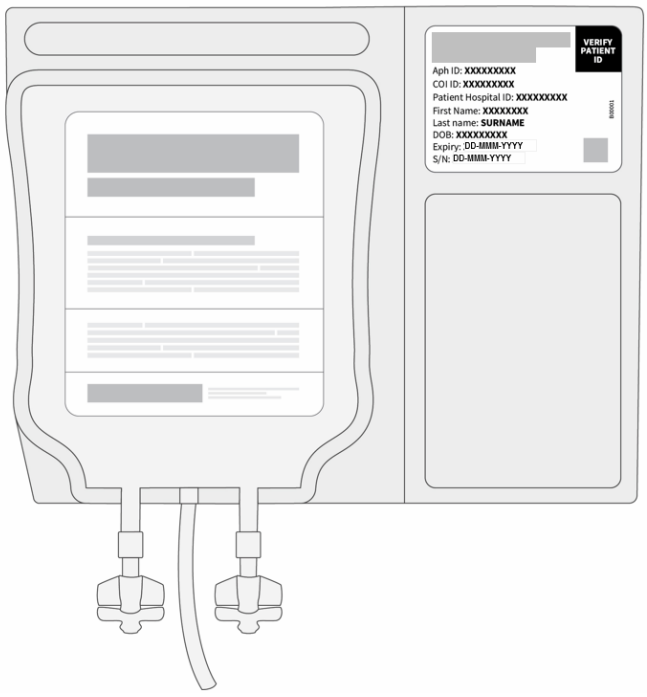
Confirm availability of Aucatzyl before starting the lymphodepleting chemotherapy regimen.

Patients should be clinically re-assessed prior to administration of lymphodepleting chemotherapy and Aucatzyl to ensure that there are no reasons to delay therapy (see section 4.4, Reasons to delay treatment).

Receipt and storage of Aucatzyl

- Aucatzyl is supplied directly to the cellular therapy laboratory associated with the infusion centre in the vapour phase of a liquid nitrogen shipper (≤ -150°C).
- Confirm the patient's identity on the infusion bags with the patient identifiers on the Release for Infusion Certificate, see Figure 2.

Figure 2: Patient Specific Identifiers



Patient Specific Identifiers:
Apheresis ID
Chain of Identity ID
Patient Hospital ID
Patient Name
Patient Date of Birth

- Keep the infusion bag(s) in the metal cassette(s) and transfer Aucatzyl to the onsite controlled-access vapour phase of liquid nitrogen for storage ≤ -150 °C (until ready for thaw and administration).
- Time out of the vapour phase liquid nitrogen environment should be kept to an absolute minimum to avoid premature product thaw (recommend not to exceed 90 seconds).

Planning prior to Aucatzyl preparation

The patient batch-specific Release for Infusion Certificate and Dose Schedule Planner will be provided in the shipper and via Autolus Scheduling Portal.

Confirm the patient identifiers on Release for Infusion Certificate and infusion bags match, Figure 2.

1. Ensure the patient's bone marrow assessment results are available (see section 4.2, Bone marrow assessment).

   NOTE: The patient's bone marrow lymphoblast assessment results will be used to select the appropriate dosing regimen: High Tumour Burden Dosage Regimen if the lymphoblast percentage is > 20% or inconclusive or Low Tumour Burden Dosage Regimen if the lymphoblast percentage is ≤ 20%.

2. The Aucatzyl Dose Schedule Planner, provided with the Release for Infusion Certificate, assists the determination of the appropriate dose regimen to be administered on Day 1 (3 days ± 1 day after the completion of lymphodepleting chemotherapy) and Day 10 (± 2 days). Record the following information on the Dose Schedule Planner:

   a. The lymphoblast percentage from the patient's bone marrow assessment
   b. The Aucatzyl bag serial number(s); number of bag type required for each dose; and the specified volume to administer via syringe (for the 10×10^6 Dose) transcribed from the Release for Infusion Certificate.

3. The completion of the Aucatzyl Dose Schedule Planner will guide the treating physician on the number of bags and the respective dose required, and the preparation of Aucatzyl for the Day 1 and Day 10 (± 2 days) dose.

Transfer and Thawing

- Using the completed Dose Schedule Planner for guidance, transfer only the cassette(s) / infusion bag(s) required for the given dosing day from the onsite vapour-phase liquid nitrogen storage to an appropriate transfer vessel (i.e., a vapour-phase liquid nitrogen shipper, maintaining temperature ≤ -150°C) for transport to the bag thaw location.
- Transfer the required cassette(s) one by one, confirming the Aucatzyl bag serial numbers and patient identifiers on each infusion bag label, see Figure 2.
- Time out of the vapour phase liquid nitrogen environment should be kept to an absolute minimum to avoid premature product thaw (recommend not to exceed 90 seconds).

- If more than one infusion bag has been required on a given dosing day, thaw each infusion bag one at a time; do not remove subsequent bags from the vapour-phase liquid nitrogen storage (≤ -150°C) until infusion of the previous bag is complete.
- Aucatzyl must be continuously monitored during the thawing process.
- Leave the Aucatzyl infusion bag in its overwrap, thaw at 37°C using a water bath or thawing device until there are no visible frozen clumps left in the infusion bag. Each bag should be gently massaged until the cells have just thawed. Thawing of each infusion bag takes between 2 to 8 minutes. Remove from the water bath or thaw device immediately after thawing is complete. Carefully remove the infusion bag from the overwrap taking care to avoid damage to the bag and ports.
- Gently mix the contents of the bag to disperse clumps of cellular material and administer immediately to the patient.
- Do not re-freeze or refrigerate thawed product.

Infusion Instructions

Aucatzyl is for autologous and intravenous use only (see section 4.4).

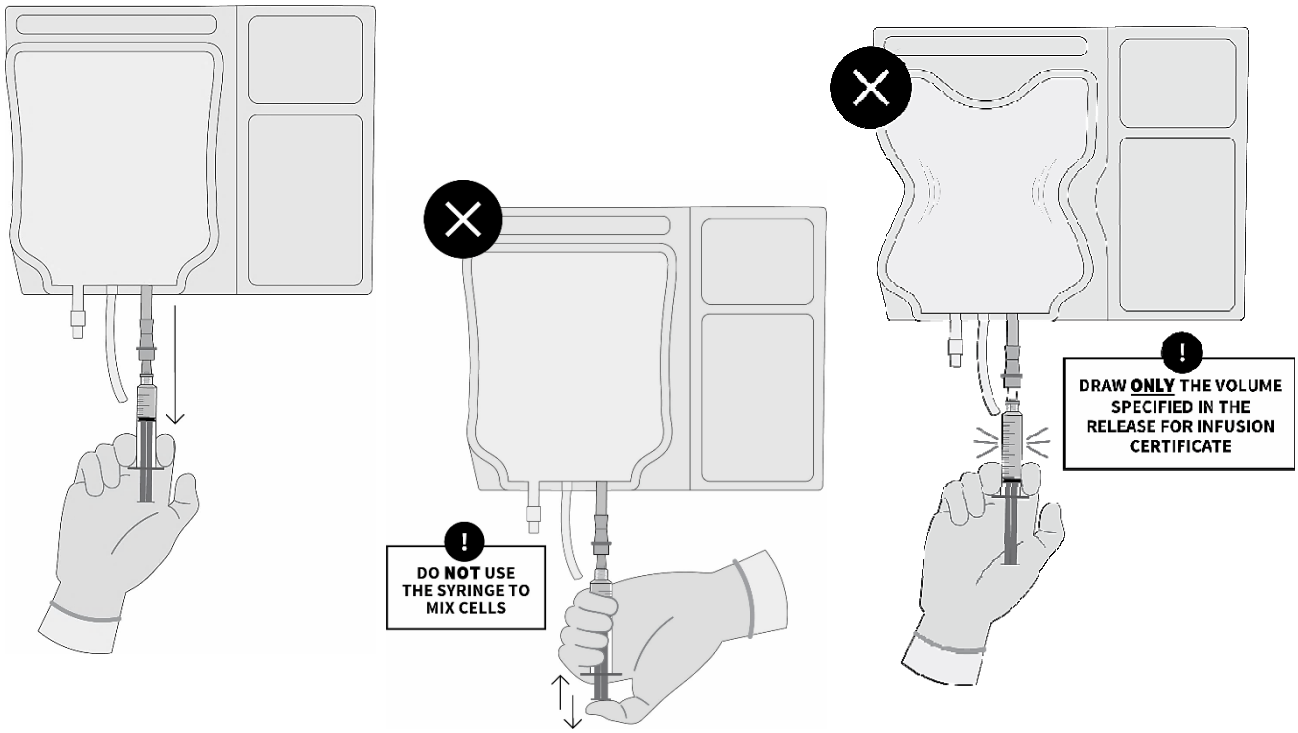
The patient's identity must match the patient identifiers on the Aucatzyl Release for Infusion Certificate and infusion bag. Contact Autolus at 00800 0825 0829 if there are any discrepancies between the labels and the patient identifiers.

Dose administration for 10×10^6 CD19 CAR-positive viable T cells (syringe-based infusion)

Withdrawal of the 10×10^6 dose into the syringe should be carried out as follows:

- Prepare and administer Aucatzyl using aseptic technique.
- Gently mix the contents of the bag to disperse clumps of cellular material.
- The volume to be administered for the 10×10^6 dose is specified on the Release for Infusion Certificate.
- Use the smallest Luer-lock tip syringe necessary (1, 3, 5, or 10 mL) with a Luer-lock bag spike to draw up the volume specified on the Release for Infusion Certificate.
    - Do not use a leukodepleting filter.
    - Do not use the syringe to mix the cells, see Figure 3.

Figure 3: Syringe Infusion Guidance for 10 × 10^6 Dose



- Prime the tubing with normal saline prior to infusion.
- Once Aucatzyl has been drawn into the syringe, verify the volume and administer as an intravenous infusion as soon as possible (as a slow push approximately 0.5 mL/minute) through a central venous line (or large peripheral venous access line appropriate for blood products).
- Complete infusion at room temperature within 60 minutes post-thaw and flush the tubing line with 60 mL of normal saline.
- Dispose of any unused portion of Aucatzyl (according to local biosafety guidelines).

Dose administration for 100 × 10^6 and/or 300 × 10^6 CD19 CAR-positive viable T cells

- Refer to the Release for Infusion Certificate for the following details:
  - The volume and total CD19 CAR-positive viable T cell number contained in each infusion bag.
  - The dose to be administered on the given dosing day and the number of bags required to deliver the specified CD19 CAR-positive viable T cell dose.
  - If more than one bag is needed, thaw subsequent bag after the previous bag is fully administered.

1. Prime the tubing with normal saline prior to infusion.
2. Administer Aucatzyl via a gravity or peristaltic pump assisted intravenous infusion through a central venous line (or large peripheral venous access line appropriate for blood products).

- Do not use a leukodepleting filter.
- Aseptic techniques must be applied when performing a venepuncture (if applicable), spiking the ports, and through cell administration process.
- Gently mix the contents of the bag during Aucatzyl infusion to disperse cell clumps.

3. Infuse the entire content of the Aucatzyl infusion bag at room temperature within 60 minutes post-thaw.
    - After the entire contents of the infusion bag is infused, rinse the bag with 30 mL of normal saline, then flush the tubing line with 60 mL of normal saline.
    - Repeat steps 1-3 for any additional infusion bags required on the given dosing day. Do not initiate thaw of the next bag until infusion of the previous bag is complete.

Measures to take in case of accidental exposure

In case of accidental exposure, local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Aucatzyl must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Aucatzyl (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

7 MARKETING AUTHORISATION HOLDER

Autolus Limited

The Mediaworks

191 Wood Lane

White City

London

W12 7FP

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 46113/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/01/2026

10 DATE OF REVISION OF THE TEXT

20/01/2026