ANNEX I

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

Strimvelis 1-10 x 10^6 cells/mL dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

An autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor ($CD34^+$) cells.

2.2 Qualitative and quantitative composition

The medicinal product is packaged in one or more infusion bags. Each patient-specific infusion bag of Strimvelis contains an autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence.

The quantitative information regarding $CD34^+$ cells/kg and total cells in the product is presented in the labelling for each batch. The concentration is 1-10 x 10^6 $CD34^+$ cells/mL.

Excipient with known effect

This medicinal product contains 0.15 mmol sodium per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.
A cloudy to clear, colourless to pink dispersion of cells.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available (see sections 4.2 and 4.4).

4.2 Posology and method of administration

Strimvelis must be administered in a specialist transplant centre, by a physician with previous experience in the treatment and management of patients with ADA-SCID and in the use of autologous $CD34^+$ *ex vivo* gene therapy products. It should only be administered after consultation with the patient and/or family. Patients are expected to enrol in a post-treatment registry and will be followed-up long term.

Strimvelis is intended for autologous use only (see section 4.4).

A $CD34^+$ stem cell back-up containing at least 1 x 10^6 $CD34^+$ cells per kg is required. This should be harvested from the patient at least 3 weeks prior to treatment with Strimvelis. The stem cell back-up is collected for use as rescue treatment should there be a failure during product manufacture, transplant failure, or prolonged bone marrow aplasia after treatment.

The patient must be able to donate sufficient $CD34^+$ cells to deliver a minimum of 4 x 10^6 purified $CD34^+$ cells/kg, required for manufacture of Strimvelis.

Before infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the medicinal product infusion bag(s) and/or container (see sections 4.4 and 6.6).

Pre-treatment conditioning
It is recommended that 0.5 mg/kg intravenous busulfan be administered every 6 hours on two consecutive days starting three days before administration of Strimvelis. The total busulfan dose is 4 mg/kg, divided into 8 doses of 0.5 mg/kg. Busulfan plasma levels should be measured after the first dose of each day by serial blood sampling using an appropriate method. If busulfan AUC exceeds 4000 nanograms/mL*h (974 μmol/L*minute), the dose should be appropriately reduced based on the AUC.

Pre-medication
It is recommended that an intravenous antihistamine be administered 15-30 minutes before the infusion of Strimvelis.

Posology

The recommended dose range of Strimvelis is between 2 and 20 x 10^6 $CD34^+$ cells/kg.

If the product contains less than 2 x 10^6 $CD34^+$ cells/kg, the treating physician should decide whether to proceed with administration, based on an individual benefit risk assessment. Treatment failure was observed in a patient treated in the clinical trials with <2 x 10^6 $CD34^+$ cell/kg.

Strimvelis should be administered once only.

Special populations

Elderly
This medicinal product is not intended for use in patients >65 years of age and has not been studied in this age group.

Renal impairment
This medicinal product has not been studied in patients with renal impairment. No dose adjustment is expected to be required.

Hepatic impairment
This medicinal product has not been studied in patients with hepatic impairment. No dose adjustment is expected to be required.

Paediatric population
The safety and efficacy of Strimvelis in children less than six months or over 6 years and 7 months of age has not been established (see section 4.4). No data are available.

Method of administration

Strimvelis is for intravenous infusion only.

Precautions to be taken before handling or administering the medicinal product

Healthcare professionals should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases when handling the product.
For instructions on preparation, accidental exposure and disposal of Strimvelis, see section 6.6.

A transfusion administration set with filter should be used. Only filters intended for use with transfusion sets should be used to prevent inadvertent removal of cells from the product.

The infusion rate should not exceed 5 mL/kg/h. The period of administration is approximately 20 minutes (see section 6.6). Following administration, a 50 mL syringe filled with a sodium chloride 9 mg/mL (0.9%) solution for injection should be used to flush the bag through.

4.3 Contraindications

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

Current or previous history of leukaemia or myelodysplasia.

Positive test for human immunodeficiency virus (HIV) or presence of any other transmissible infectious agent listed in the current EU Cell and Tissue Directive prior to bone marrow harvest.

History of previous gene therapy.

4.4 Special warnings and precautions for use

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 should be kept for a period of 30 years.

Autologous use

Strimvelis is intended solely for autologous use and should never be administered to any patient other than the original $CD34^+$ cell donor.

Risk of insertional oncogenesis

One case of Lymphoid T cell leukaemia has been reported in a child with ADA-SCID 4.7 years after treatment with Strimvelis (see section 4.8).
It is recommended that patients be monitored long term with at least annual visits for the first eleven years and then at 13 and 15 years post treatment with Strimvelis, to include a complete blood count with differential, biochemistry and thyroid stimulating hormone.

General

The long-term effects and durability of response to Strimvelis on ADA-SCID have not been systematically assessed beyond 8 years after treatment (see section 5.1).

Non-immunological manifestations of ADA-SCID may not respond to Strimvelis.

Cases of skin papillomas, abnormal serum protein electrophoresis and one case each of lipofibroma, pulmonary mass and decreased T-cell V beta repertoire were reported. No evidence of causality of the product has been established.

In some cases, the patient may be unable to receive treatment because of manufacturing issues. After notification, the treating physician may need to modify the treatment program of the patient accordingly (i.e.

terminating the busulfan conditioning and/or administration of the stem cell back up treatment if appropriate).

Warnings and precautions of the myeloablative conditioning medicinal products must be considered.

Immune reconstitution

During the clinical studies, T-lymphocyte ($CD3^+$) and NK ($CD56^+$) cell counts improved following treatment. Median values at 3-years post gene therapy were below the normal range. Continued follow-up is recommended.

Central venous catheter (CVC) complications including infections and thromboses

Adverse events related to the use of central venous catheters (CVCs) have been reported (e.g., serious CVC infections and thrombosis in the device). Patients should be closely monitored for potential catheter-related events.

Hypersensitivity and infusion-related reactions

This medicinal product should be used with caution in patients with hypersensitivity to aminoglycosides or bovine serum albumin.

Engraftment failure

There have been cases where treatment has been unsuccessful. Some patients have had to resume long-term enzyme replacement therapy and/or receive a stem cell transplant (see section 5.1).
Patients should be closely monitored for the occurrence of severe and opportunistic infections, immune reconstitution parameters and the need for replacement intravenous immunoglobulin (IVIG); in case of lack of response, it is recommended to introduce other ADA-SCID treatments under the supervision of a physician.

Transmission of an infectious agent

A small risk of transmission of infectious agents exists. Healthcare professionals administering Strimvelis should therefore monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Autoimmunity and immunogenicity

Patients with ADA-SCID can develop autoimmunity. In clinical studies, 67% (12 of 18) of treated patients had either autoimmune antibodies or other manifestations (e.g. autoimmune thrombocytopenia, autoimmune aplastic anaemia, autoimmune hepatitis and Guillain-Barré syndrome) (see section 4.8). Regular monitoring for clinical autoimmunity is recommended.
No immunogenicity testing has been conducted with Strimvelis.

Treatment of patients younger than 6 months and older than 6 years and 7 months

The treatment should be used with caution in patients younger than 6 months and older than 6 years and 7 months as there are no clinical data in these age ranges. Older patients are typically less able to donate high numbers of $CD34^+$ cells which may mean that older patients cannot be treated. Successful generation of T cells after treatment is also likely to be affected by residual thymic function which can become impaired in older children. Use of this medicinal product in patients older than those previously studied should be carefully considered and reserved only for occasions where all other reasonable treatment options have been exhausted.

Serological testing

All patients should be tested for HIV-1/2, HTLV-1/2, HBV, HCV and mycoplasma prior to bone marrow harvest to ensure acceptance of the cellular source material for Strimvelis manufacturing.
Patients who have previously tested positive for hepatitis C can be treated with Strimvelis, provided they demonstrate absence of ongoing infection using a nucleic acid test with a limit of quantification of ≤15 international units/mL. Negative test results are required on at least 3 sequential occasions over a period of at least 4 weeks, after completion of treatment for hepatitis C, with the final test conducted no more than 3 days prior to cell harvest.

Blood, organ, tissue and cell donation

Patients treated with Strimvelis should not donate blood, organs, tissues and cells for transplantation, at any time in the future. This information is provided in the Patient Alert Card.

After Strimvelis administration

Stage two quality control results will only be available after the product has been infused. If clinically relevant quality issues, such as out of specification results, are identified after the medicinal product has been infused, the treating physician will be notified. The physician should monitor and/or treat the patient as appropriate.

Sodium content

This medicinal product contains 42 to 137 mg sodium per dose, which is equivalent to 2 to 7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Strimvelis is not expected to interact with the hepatic cytochrome P-450 family of enzymes or drug transporters.

Live vaccines

The safety of immunisation with live viral vaccines following Strimvelis treatment has not been studied. Vaccination with live virus vaccines is not recommended during the 6 weeks preceding the start of non-myeloablative conditioning, and until haematological and immunological recovery following treatment with Strimvelis.

4.6 Fertility, pregnancy and lactation

As Strimvelis is not intended for use in adults, human data on use during pregnancy or lactation and animal reproduction studies are not available.
With regard to fertility, consult the SmPC of the conditioning medicinal product. It should be noted that the treating physician should inform the patient's parents/carers about options for cryopreservation of spermatogonial stem cells or ovarian tissue.

4.7 Effects on ability to drive and use machines

Strimvelis has no or negligible long-term influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Strimvelis was evaluated in 33 subjects i.e. 22 patients treated in the clinical development program and 11 patients treated in the commercial setting, with a median duration of follow-up of 12 years for patients treated in clinical studies and 1.5 years for patients treated in the commercial setting.
Given the small patient population and size of the cohorts, adverse reactions in the table below may not provide a complete perspective on the nature and frequency of these events. Serious adverse reactions include T-cell type acute leukaemia and autoimmunity (e.g. autoimmune haemolytic anaemia, autoimmune aplastic anaemia, autoimmune hepatitis, autoimmune thrombocytopenia and Guillain-Barré syndrome). The most commonly reported adverse reaction was pyrexia.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories used are: very common (≥1/10), and common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common
Blood and lymphatic system disorders	Anaemia[a], neutropenia[a]	Autoimmune haemolytic anaemia, autoimmune aplastic anaemia, autoimmune thrombocytopenia
Endocrine disorders	Hypothyroidism	Autoimmune thyroiditis
Neoplasms, benign, malignant and unspecified		T-cell type acute leukaemia
Nervous system disorders		Guillain-Barré syndrome
Vascular disorders	Hypertension[a]	
Respiratory, thoracic and mediastinal disorders	Asthma, rhinitis allergic	
Hepatobiliary disorders		Autoimmune hepatitis
Skin and subcutaneous tissue disorders	Dermatitis atopic, eczema	
General disorders and administration site conditions	Pyrexia	
Investigations	Hepatic enzyme increased[a], antinuclear antibody (ANA) positive, smooth muscle antibody positive	Antineutrophil cytoplasmic antibody positive

[a]Adverse reactions considered potentially related to busulfan conditioning

Description of selected adverse reactions

Lymphoid T cells leukaemia due to insertional oncogenesis
Out of 33 patients with ADA-SCID treated with Strimvelis, one case of Lymphoid T cell leukaemia has been reported in one child (frequency: 3%). This event occurred 4.7 years after treatment with Strimvelis. Retroviral insertion site (RIS) analysis identified a single dominant clone located approximately 40 kb upstream of the LMO2 gene, a known oncogene, with an abundance ≥ 98%.

Immune reconstitution
All the identified adverse reactions in the table (apart from those potentially related to busulfan) are considered to be related to immune reconstitution, due to their nature and timing. These autoimmune adverse reactions were reported for subjects post-gene therapy. The majority were reported during the 3-month to 3-year follow-up period and resolved, with the exception of hypothyroidism and positive ANA tests. In addition, the allergy related adverse reactions in the table were reported mostly during the 3-month to 3-year follow-up period.

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 the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of Strimvelis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, other immunostimulants, ATC code: L03AX.

Mechanism of action

After infusion, $CD34^+$ cells engraft in the bone marrow where they repopulate the haematopoetic system with a proportion of cells that express pharmacologically active levels of the ADA enzyme.

Following successful engraftment in the patient, the effects of the product are expected to be life-long.

Pharmacodynamic effects

The median percentages of genetically modified cells in peripheral blood at one year and 3 years after treatment, for the patients enrolled in the pivotal study, were 28% (range 6%-92%) and 30% (range 8%-101%) of CD19+, and 73% (range 20%-100%) and 67% (range 39%-82%) of CD3+ cells, respectively. The median percentages of genetically modified cells in peripheral blood at year 8 for the patients enrolled in the long-term follow-up were 97% (range 1%-101%) of CD19+, and 101% (range 1%-101%) of CD3+ cells.

The presence of the transgene leads to increased expression of ADA. One-year post treatment, median ADA activity (mononuclear cells adenosine deaminase) in peripheral blood lymphocytes was 181.2 (range 42.1-1678.2) nmol/h/mg protein, compared to a baseline median (range) of 80.6 (30.5-92.3) nmol/h/mg protein. ADA activity remained increased throughout the duration of the 8 year follow up.

Clinical efficacy and safety

A total of 18 patients with ADA-SCID were treated with Strimvelis as part of one open-label pivotal trial (AD1115611; N=12), two early open-label pilot studies (AD1117054/AD1117056; N=3), and a compassionate use program (AD1117064; N=3). Studies evaluated the use of Strimvelis with a range of 0.9×10^6 - 18.2×10^6 $CD34^+$ cells/kg. All patients received busulfan conditioning prior to gene therapy, with most receiving a total dose of 4 mg/kg intravenously over 2 consecutive days prior to $CD34^+$ infusion. Four subjects had previously received an unsuccessful stem cell transplant from a haploidentical donor and 15 of 18 subjects had previously received prior enzyme replacement therapy with polyethylene-glycol-modified bovine adenosine deaminase (PEG-ADA). Patients who previously received PEG-ADA had this treatment

withdrawn 10 to 22 days prior to Strimvelis therapy. The median age across the program was 1.7 years (range 0.5 to 6.1) and 61% were males. Eighty three percent were white (56% Caucasian/European heritage and 28% Arabic/North African heritage), 11% African American/African, and 6% Asian.

Patients treated within the pivotal study
The efficacy of Strimvelis was evaluated in a 3-year open-label, prospective study in children who lacked a sibling HLA matched stem cell donor and were either failing to respond adequately to PEG-ADA, were intolerant or did not have access to it.

Results at 3 years for patients treated within the pivotal study are presented in Table 1. Treatment with Strimvelis resulted in a 100% survival rate at 3 years post therapy, a decrease in the severe infection rate, an increase in T-lymphocytes (CD3+) and all subjects having post-baseline venous red blood cell deoxyadenosine nucleotide (RBC dAXP) levels below pathological levels (>100 nmol/mL).

Table 1. Results at 3 years for the ITT population in the pivotal study*

Endpoint	**Baseline/ Pre-Treatment[a]**	**Year 3/ 3 Years Post-Treatment[b]**
Survival n %	Not applicable	12 100%
Severe infections n Rate of severe infections per person-year of observation (95% confidence interval)	12 1.01 (0.68-1.46)	12 0.38[c] (0.21-0.65)
T-lymphocyte (x10^6/L) n median (range)	11 88.0 (19-2718)	11 828.0 (309-2458)
% subjects with venous RBC dAXP <100 nmol/mL after Strimvelis[d] n %	Not applicable[e]	11 100%

* Including data from one patient collected post intervention with PEG-ADA (≥3 months treatment) or hematopoietic stem cell transplantation

[a] Based on the entire pre-treatment period for severe infections (retrospectively collected), and the data collected at the baseline visit for T-lymphocytes. Patient 10 had no baseline value for T-lymphocytes.

[b] Based on the 3-year post-treatment period for survival and severe infections, and the data collected at the 3-year visit for T-lymphocytes and dAXP. Patient 8 withdrew from the study before 3-year visit, and thus had no data for T-lymphocytes and dAXP.

[c] Severe infections are those requiring or prolonging hospitalisation. The 3-month hospitalisation period immediately post gene therapy was excluded from the calculation

[d] dAXP=dAMP+dADP+dATP. dAXP results are based on a responder analysis of the percentage of patients following gene therapy who met the definition of adequate metabolic detoxification, therefore baseline value is not applicable.

[e] At baseline 9 of 11 (82%) patients had dAXP <100 nmol/mL. All these patients had previously taken PEG-ADA.

T cell function: In the patients treated in the pivotal study, T cell proliferation was demonstrated in response to stimulation with anti-CD3 antibodies (median 62629 cpm, range 4531 to 252173) and phytohemaglutinin (median 140642 cpm, range 11119 to 505607) at 1 year post gene therapy, and these responses were sustained through Year 3. Findings that TREC (T cell receptor excision circles) in peripheral blood lymphocytes were increased above baseline (median 141, range 56 to 1542 copies/100 ng DNA) at Years 1 and maintained to 3 post-treatment and that all subjects had evidence of polyclonal V-beta chains at one or more time points following gene therapy provides further supportive evidence of functional T cell development.

B cell function: All 12 subjects treated in the pivotal study were receiving IVIG therapy at the time of screening, and 7 subjects (58%) had discontinued IVIG use during 0-3 years follow-up after gene therapy.

Long-term follow-up
A 100% survival rate was observed for all 12 subjects treated within the pivotal study and also for the 18 subjects in the integrated analysis, with a median follow up duration of approximately 12 years. Intervention-free survival in this pivotal population (defined as survival without the requirement for long-term (≥3 month) re-introduction of PEG-ADA, or stem cell transplant) was 92% (11/12 subjects) (82% (14/17 subjects) for integrated population). One subject treated in a pilot study did not have PEG-ADA re-introduction data, and thus was excluded from the intervention-free survival in the integrated population. Long-term PEG-ADA (exceeding 3 months of continuous duration) was used by three subjects; two of these subjects subsequently received a sibling-matched stem cell transplant and one subject remained on chronic PEG-ADA treatment. Another subject needed transient PEG-ADA administration due to an autoimmune event (see section 4.4).

In those patients treated in the pivotal and long-term follow-up (LTFU) study, the rate of severe infections declined throughout the follow-up period (Table 2).

Table 2 Cumulative rate of severe infections per person year of exposure (combined pivotal and LTFU ITT population)*

	Pre treatment	Post treatment							
Time period	n/a	3 mths – 1 year	Up to 2 years	Up to 3 years	Up to 4 years	Up to 5 years	Up to 6 years	Up to 7 years	Up to 8 years
No. of subjects	17	17	17	17	16	15	15	15	15
No. of severe infections	40	11	18	18	20	20	21	21	21
Rate of severe infections per person year	1.08	0.73	0.56	0.35	0.30	0.24	0.22	0.19	0.17

* Excluding data from one patient from the Pilot 1 study who was not followed up until year 13 after gene therapy.
n/a: not applicable.

5.2 Pharmacokinetic properties

Strimvelis is an autologous cellular therapy. The nature of Strimvelis is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

5.3 Preclinical safety data

Reproductive and developmental studies have not been conducted.

A 4-month biodistribution study was performed in mice. $CD34^+$ cells derived from healthy human umbilical cord blood, transduced with the vector used for the production of Strimvelis, were administered intravenously to busulfan-conditioned mice. The majority of mice showed reconstitution of the haematopoietic system by the end of the study. Low levels of human cells and vector sequences were also detected in non-haematopoietic organs consistent with the presence of blood containing transduced human cells. There were no adverse reactions on survival, haematological parameters or histopathology of major

organs, apart from body weight loss and atrophy in the testes and ovaries consistent with administration of busulfan.

Carcinogenicity studies have not been conducted as no adequate animal model was available to evaluate the tumourigenic potential of Strimvelis due to the inability to achieve long-term engraftment of transduced cells in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

24 hours

Once removed from refrigerated condition, maximum 90 minutes (15 °C-25 °C).

6.4 Special precautions for storage

Store at refrigerated condition (2 °C-8 °C) until the patient is ready for treatment.

Do not refrigerate (2 °C-8 °C) after carrying at room temperature (15 °C-25 °C).

6.5 Nature and contents of container

50 mL ethylene vinyl acetate (EVA) infusion bag, with a luer spike interconnector closed with a luer lock cap, packed in a re-usable outer container.

6.6 Special precautions for disposal and other handling

Precautions to be taken when handling or administering the medicinal product

Healthcare professionals handling Strimvelis should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Strimvelis is transported directly to the medical facility where the infusion will be administered. The infusion bag(s) is/are placed inside a closed outer container. The bags must be kept in the outer container until ready to use.

Strimvelis is intended solely for autologous use. The identity of the patient must be matched with the essential unique patient information on the primary and/or outer container prior to infusion.

After careful removal from the metal cassette, warm up at room temperature (15 °C - 25 °C) the infusion bag in its sealed overwrap bag under laminar flow hood for at least 7 minutes. Gently agitate the infusion bag to re-disperse any cellular aggregates, administer using a transfusion administration set with filter to remove any remaining cellular aggregates.

Precautions to be taken for the disposal of the medicinal product

Local guidelines on handling human-derived material should be followed for unused medicinal product or waste material. All material that has been in contact with Strimvelis (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.

Accidental exposure

Accidental exposure to Strimvelis must be avoided. Local guidelines on handling of human derived materials should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Strimvelis must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

Fondazione Telethon ETS
Via Varese 16/B
00185 Rome
Italy

8. MARKETING AUTHORISATION NUMBER

EU/1/16/1097/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2016
Date of latest renewal: 30 April 2021

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

AGC Biologics S.p.A.
3 Via Antonio Meucci
20091
Bresso
Italy

Name and address of the manufacturer responsible for batch release

AGC Biologics S.p.A.
3 Via Antonio Meucci
20091
Bresso
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Strimvelis in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials for parents/carers and health professionals,

restricted prescription details and controlled access/product consent form, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

Strimvelis will be administered at a specialist transplant centre, and by physicians with previous experience in the treatment and management of patients with ADA-SCID and the use of autologous CD34+ *ex vivo* gene therapy products. A completed product consent form is required prior to initiating treatment.

The educational materials should address the following safety concerns/key elements: Autoimmunity, Unsuccessful response to gene therapy, and Malignancy due to insertional oncogenesis (e.g. leukaemia, myelodysplasia).

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measure:

Description	**Due date**
Non-interventional PASS: In order to investigate the long term safety and efficacy of Strimvelis gene therapy, the MAH should conduct and submit the results of a long term prospective, non-interventional follow up study using data from a registry of patients with adenosine deaminase severe combined immunodeficiency (ADA-SCID) treated with Strimvelis. The MAH will follow up on the risk of immunogenicity, insertional mutagenesis and oncogenesis as well as hepatic toxicity. The MAH will review the occurrence of angioedema, anaphylactic reactions, systemic allergic events and severe cutaneous adverse reactions during the FU period, particularly in those patients who had unsuccessful response and received ERT or SCT. The MAH will also evaluate intervention-free survival.	The MAH shall plan to include regular progress reports of the registry in the PSUR and provide interim study reports every 2 years until the registry finishes. Interim registry reports shall be submitted every 2 years. The final clinical study report should be submitted after the 50th patient has 15 year follow-up visit; Q2 2046.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Strimvelis 1-10 x 10^6 cells/mL dispersion for infusion.

2. STATEMENT OF ACTIVE SUBSTANCE

An autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence with a concentration of 1-10 x 10^6 $CD34^+$ cells/mL.

3. LIST OF EXCIPIENTS

Also contains sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion.
No. of infusion bags:

Total cell number: x 10^6
$CD34^+$ cells/kg: x 10^6

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP {DD/MM/YYYY} {hh:mm}

Shelf life once removed from refrigerated condition: 90 minutes at room temperature (15 °C-25 °C)

9. SPECIAL STORAGE CONDITIONS

Store and transport at refrigerated condition (2 °C-8 °C)
Keep infusion bag in the metal cassette until ready for administration. Once carried at room temperature (15 °C-25 °C) do not re-refrigerate (2 °C-8 °C).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically-modified human cells.
Local guidelines on handling human-derived material should be followed for unused medicinal product or waste material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fondazione Telethon ETS
Via Varese 16/B
00185 Rome
Italy

12. MARKETING AUTHORISATION NUMBER

EU/1/16/1097/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot
Patient ID:
DIN:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Strimvelis 1-10 x 10^6 cells/mL dispersion for infusion.
For intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {DD/MM/YYYYY} {hh:mm}

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot
Bag No.:
Patient ID:
DIN:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Total cell number: x 10^6
$CD34^+$ cells/kg: x 10^6

6. OTHER

For autologous use only.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient or carer

Strimvelis 1-10 × 10^6 cells/mL dispersion for infusion

Autologous $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child is given this medicine because it contains important information for your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or nurse.
- If your child gets any side effects, talk to your child's doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Your child's doctor will give you a Patient Alert Card which contains important safety information about your child's treatment with Strimvelis. Read it carefully and follow the instructions on it.
- Carry the Patient Alert Card with you at all times and always show it to the doctor or nurse when your child sees them or if your child goes to hospital.

What is in this leaflet

1. What Strimvelis is and what it is used for

Strimvelis is a type of medicine called a **gene therapy**. It is made specially for each patient.

Strimvelis is used in children to treat a serious condition called **ADA-SCID** (a*denosine deaminase-severe combined immune deficiency*). It is used when your child cannot receive a bone marrow transplant from a family donor because the match is not close enough.

ADA-SCID occurs because of a faulty gene in the blood cells of your child's immune system. As a result, the cells do not produce enough of an enzyme called *adenosine deaminase* (ADA) and your child's immune system does not work properly to defend the body against infections.

To make Strimvelis, stem cells from your child's bone marrow are modified in the laboratory to insert a gene that produces ADA. When these modified stem cells are given back to your child, they can divide to produce different types of blood cells, including cells involved in your child's immune system.

2. What you need to know before you (or your child) are given Strimvelis

Strimvelis is not suitable for some people

Strimvelis must not be given if your child:
- is **allergic** to any of the ingredients of this medicine (*listed in section 6*)

- has or has had a type of **cancer** called *leukaemia* or *myelodysplasia*
- has tested positive for **HIV or some other infections** (your doctor will advise you about this)
- has already been treated with **gene therapy**

Warnings and precautions

Information about cell-based medicinal products, like Strimvelis, must be kept for 30 years at the hospital. The information kept about your child will be your child's name and the batch number of Strimvelis your child received.

Strimvelis is made specially from the patient's own cells. It must never be given to anyone else.

Inserting a new gene into the DNA could cause blood cancer. There has been a case of blood cancer, called leukaemia in one patient several years after treatment with Strimvelis. It is therefore important to monitor your child for the symptoms of leukaemia.
These include fever, shortness of breath, paleness, night sweats, tiredness, swollen lymph glands, frequent infections, a tendency to bleed and/or bruise easily, or tiny red or purple spots under the skin. If your child develops any of these symptoms you should contact your doctor immediately.

Before treatment with Strimvelis, your child will be given other medicines (see sections 3 and 4 for more information on these medicines, including possible side effects).

If your child has previously tested positive for hepatitis C, your child can still be treated under certain conditions. Your doctor will discuss this with you if needed.

Central venous catheters are thin, flexible tubes, that are inserted by a doctor into a large vein to access the bloodstream of your child. The risks of these lines are infections and the formation of blood clots. The doctor and nurses will monitor your child for any central venous catheter complications.

Treatment with Strimvelis has been unsuccessful in some patients. These patients received alternative treatment options.

There is a small risk of infection as a result of the treatment. Your child's doctors and nurses will monitor them throughout the infusion for signs of infection and provide treatment if needed.

Some patients can develop autoimmunity i.e. trigger an immune response against their own cells or tissues (see section 4). Your child's doctor will discuss this with you if needed.

After the treatment, your child must not donate blood, organs, tissues or cells at any time in future. This is because Strimvelis is a gene therapy product.

When Strimvelis treatment cannot be completed
In some cases, it might not be possible to go ahead with the planned treatment with Strimvelis for reasons such as:

- a problem taking the cells from your child's bone marrow to make the medicine
- not enough of the right type of cells in the tissue taken from your child's body to make the medicine
- the medicine not meeting all the quality tests
- a delay in the medicine reaching the clinic where your child is being treated.

Before receiving Strimvelis your child will be given chemotherapy in order to remove their existing bone marrow. If Strimvelis cannot be administered after chemotherapy or if the modified stem cells do not take hold (engraft) in your child's body, the doctor will give your child replacement stem cells, using the backup sample that was collected and stored before treatment started (*see also section 3, How Strimvelis is given*).

You may need other treatment

Strimvelis goes through a range of tests before it is used. Because it is given soon after it is made, the final results of some of these tests will not be ready before the medicine is given. If the tests show anything that might affect your child, the doctor will treat your child as appropriate.

Other medicines and Strimvelis
Tell your doctor if your child is taking, has recently taken or might take any other medicines.

Your child must not be given vaccines called live vaccines for 6 weeks before they are given the conditioning medicine to prepare for Strimvelis treatment, nor after treatment while your child's immune system is recovering.

Strimvelis contains sodium
This medicine contains 42 to 137 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 2 to 7% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Strimvelis is given

Strimvelis is given by a drip *(infusion)* into a vein *(intravenously)*. It must be given in a specialised hospital, and by a doctor who is experienced in treating patients with ADA-SCID and in using this type of medicine.

Before Strimvelis is made, the doctor will do tests to make sure that your child is not carrying certain infections (see section 2).

Two samples are collected
The doctor will collect two samples of bone marrow cells before the planned treatment:

- the **backup sample**, collected at least 3 weeks before Strimvelis treatment. It will be stored, to be given as replacement cells if Strimvelis cannot be given or does not work *(see 'When Strimvelis treatment cannot be completed' in section 2)*
- the **treatment sample**, collected 4 to 5 days before Strimvelis treatment. It will be used to make Strimvelis, by inserting a new gene into the cells.

Before and during Strimvelis treatment

When	**What is done**	**Why**
At least 3 weeks before treatment	Backup sample of stem cells collected	to be stored as a backup *(see above)*
About 4 to 5 days before treatment	Treatment sample of stem cells collected	to make Strimvelis *(see above)*
3 days and 2 days before treatment	A medicine called busulfan is given 4 times a day for 2 days (total of 8 doses)	to prepare the bone marrow for Strimvelis treatment and clear existing stem cells
About 15 to 30 minutes before treatment	An antihistamine medicine may be given	to make it less likely that you will react to the infusion
Strimvelis is given…	by a drip into a vein. This will take about 20 minutes	

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side-effects linked to Strimvelis are caused by the immune system becoming over-active and attacking the body's own tissues. Some side effects may also be related to the busulfan medicine used to prepare your child's bone marrow for treatment; these are marked with an asterisk (*) in the list below.

Very common: may affect more than 1 in 10 people:

- runny or blocked nose (*allergic rhinitis*)
- wheezing, difficulty breathing (*asthma)*
- inflamed itchy skin (*atopic dermatitis, eczema*)
- raised temperature (*pyrexia*)
- underactive thyroid gland (*hypothyroidism*)
- high blood pressure (*hypertension*)*
- decreases in the number of red or white blood cells (*anaemia, neutropenia*)*
- increases in liver enzymes (which indicate stress on the liver)*
- blood test results positive for *antinuclear antibody* and *smooth muscle antibody* (which might suggest possible autoimmunity)

C**ommon: may affect up to 1 in 10 people**.

- red or purple dots on the skin, bleeding under the skin (*autoimmune thrombocytopenia*)
- inflamed thyroid gland (*autoimmune thyroiditis*)
- weakness and pain in the feet and hands caused by damage to nerves (*Guillain-Barré syndrome*)
- inflamed liver (*autoimmune hepatitis*)
- reduced numbers of blood cells (*autoimmune haemolytic anaemia, autoimmune aplastic anaemia*)
- blood test results positive for *antineutrophil cytoplasmic antibody* (which could lead to autoimmune inflammation and swelling of the blood vessels and possibly increased level of infections)
- a type of blood cancer called leukaemia

If you have any questions about symptoms or side effects, or if any symptoms concern you, talk to your child's doctor or nurse.

Reporting of side effects
If your child gets any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Strimvelis

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date and time (EXP) which is stated on the container label and infusion bag label.

Store at refrigerated condition (2 °C-8 °C) for up to 24 hours.

Keep infusion bag in the metal cassette until ready for administration. Once removed from refrigerated condition, store at room temperature (15 °C-25 °C) for up to 90 minutes and do not re-refrigerate.

This medicine contains genetically-modified human cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling human-derived material. As this medicine will be given by a qualified doctor, they are responsible for correct disposal of the product. These measures will help protect the environment.

6. Contents of the pack and other information

What Strimvelis contains

- The active substance is an autologous (the patient's own) $CD34^+$ enriched cell fraction that contains $CD34^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence. The concentration is 1-10 × 10^6 $CD34^+$ cells/mL.
- The other ingredient is sodium chloride (see section 2, "Strimvelis contains sodium").

What Strimvelis looks like and contents of the pack

Strimvelis is a cloudy to clear, colourless to pink dispersion of cells for infusion, which is supplied in one or more infusion bags. The infusion bags are provided in a closed container.

Marketing Authorisation Holder

Fondazione Telethon ETS
Via Varese 16/B
00185 Rome
Italy

Manufacturer

AGC Biologics S.p.A.
3 Via Antonio Meucci
20091
Bresso
Italy

This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Precautions to be taken when handling or administering the medicinal product

Healthcare professionals handling Strimvelis should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Strimvelis is transported directly to the medical facility where the infusion will be administered. The infusion bag(s) is/are placed inside a closed outer container. The bags must be kept in the outer container until ready to use.

Strimvelis is intended solely for autologous use. The identity of the patient must be matched with the essential unique patient information on the primary and/or outer container prior to infusion.

Gently agitate the infusion bag to re-disperse any cellular aggregates, administer using a transfusion administration set with filter to remove any remaining cellular aggregates.

Precautions to be taken for the disposal of the medicinal product

Local guidelines on handling human-derived material should be followed for unused medicinal product or waste material. All material that has been in contact with Strimvelis (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.

Accidental exposure

Accidental exposure to Strimvelis must be avoided. Local guidelines on handling of human derived materials should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Strimvelis must be decontaminated with appropriate disinfectant.