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 million 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 finished product is composed of one or more ethylene vinyl acetate (EVA) bags which contain 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 million $CD34^+$ cells/ml.

Excipient with known effect

This medicinal product contains 0.15 mmol sodium per ml (see section 4.4).

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 section 4.2 and section 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. Strimvelis 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.

A $CD34^+$ stem cell back-up containing at least 1 million $CD34^+$ 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 with Strimvelis.

The patient must be able to donate adequate $CD34^+$ cells to deliver the minimum 4 million purified $CD34^+$ cells/kg, required for manufacture of Strimvelis.

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

Before infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the Strimvelis 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.

Premedication
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 million $CD34^+$ cells/kg.

If the product contains less than 2 million $CD34^+$ cells/kg, the treating physician should make a decision 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 millions $CD34^+$cell/kg.

Strimvelis should be administered once only.

Special populations

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

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

Hepatic impairment
Strimvelis 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 of age or over 6 years 1 month has not been established (see section 4.4). No data are available.

Method of administration

Strimvelis is for intravenous infusion.

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 saline filled 50 ml syringe should be used to flush the bag through.

Precautions to be taken before manipulating or administering the product

This medicinal product contains genetically-modified cells. Local biosafety guidelines applicable for such products should be followed (see section 6.6).

Strimvelis is not tested for transmissible infectious agents. Healthcare professionals handling Strimvelis should therefore take appropriate precautions to avoid potential transmission of infectious diseases.

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

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

In some cases the patient may be unable to receive Strimvelis 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).

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 Strimvelis has been infused, the treating physician will be notified. The physician should monitor and/or treat the patient as appropriate.

Strimvelis should be used with caution in patients older than 6 years and 1 month and younger than 6 months as there are no data from clinical trials 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 Strimvelis is also likely to be affected by residual thymic function which can become impaired in older children. Use of Strimvelis 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.

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.

Strimvelis should be used with caution in patients with hypersensitivity to aminoglycosides or bovine serum albumin.

No cases of leukaemia or myelodysplasia have been reported following treatment with Strimvelis. However, vector insertions into chromosomal regions previously associated with leukaemia in comparable trials of gene therapy in Wiskott Aldrich Syndrome, X-SCID and Chronic Granulomatous Disease have been documented. Retroviral insertion sites (RIS) have been detected adjacent to or within CCND2 and LMO2 and there is a potential risk of leukaemic transformation following treatment with Strimvelis. 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.

The long term effects and durability of response to Strimvelis on ADA-SCID are unknown (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.

There have been cases where treatment with Strimvelis 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).

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

No immunogenicity testing has been conducted with Strimvelis.

Patients can develop autoimmunity. 67% (12 of 18) of Strimvelis 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).

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.

T-lymphocyte (CD3+) and NK (CD56+) cell counts improved following treatment with Strimvelis. Median values at 3 years post gene therapy were below the normal range. Continued follow-up is recommended. 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 to the product has been established.

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.

Sodium content
This medicinal product contains 0.15 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
As Strimvelis will be administered following busulfan conditioning, patients of childbearing potential must use reliable barrier contraception during administration of Strimvelis and for at least 6 months afterwards.

Pregnancy
No clinical data on exposed pregnancies are available.
Reproductive and developmental toxicity studies were not performed.

Strimvelis should not be used during pregnancy.

Breast-feeding
It is unknown whether Strimvelis is excreted in human milk. The effect on breast-fed infants of administration of Strimvelis to their mothers has not been studied.

Strimvelis should not be administered to women who are breast-feeding.

Fertility
There are no data on the effects of Strimvelis on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

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 18 subjects, with a median duration of follow-up of 12 years. Given the small patient population and size of the cohorts, adverse reactions in the table do not provide a complete perspective on the nature and frequency of these events. Serious adverse reactions include 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 $\geq 1/10$
Common $\geq 1/100$ 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
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

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: not yet assigned

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 million – 18.2 million $CD34^+$ 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	 12	 12

Rate of severe infections per person-year of observation (95% confidence interval)	1.10 (0.74-1.58)	0.429 [c] (0.24-0.72)
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/100ng 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	32	11	18	18	20	20	21	21	21
Rate of severe infections per person year	0.86	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 effects 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

6 hours.

6.4 Special precautions for storage

Store at 15-30°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

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.

This medicinal product contains genetically-modified cells. Local biosafety guidelines applicable should be followed (see section 4.2).

Strimvelis is not tested for transmissible infectious agents. Healthcare professionals handling Strimvelis should therefore take appropriate precautions to avoid potential transmission of infectious diseases.

Work surfaces and material which have potentially been in contact with Strimvelis must be decontaminated with appropriate disinfectant.

Any unused medicinal product or waste material should be disposed of in accordance with local biosafety requirements.

7. MARKETING AUTHORISATION HOLDER

Orchard Therapeutics (Netherlands) BV
Prins Bernhardplein 200,
1097 JB Amsterdam,
the Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1097/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2016

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 http://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
MolMed SpA
58 Via Olgettina
20132
Milan
Italy

Name and address of the manufacturer responsible for batch release
MolMed SpA
58 Via Olgettina
20132
Milan
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**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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; Q4 2037.

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 million cells/ml dispersion for infusion.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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 million $CD34^+$ 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(S) 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(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

Exp.: {DD MMM YY} {hh:mm}

9. SPECIAL STORAGE CONDITIONS

Store at 15-30°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 cells.
Unused medicine must be disposed of in compliance with the local biosafety guidelines.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchard Therapeutics (Netherlands) BV
Prins Bernhardplein 200,
1097 JB Amsterdam,
the Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1097/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Patient ID:

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(S) OF ADMINISTRATION

Strimvelis 1-10 million cells/ml dispersion for infusion.
For intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp.: {DD MMM YY} {hh:mm}

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Patient ID:
Bag No.:

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 million 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 you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you (or your child) are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you (or your child) get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to your doctor or nurse when you see them or if you go 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**.

Strimvelis is used to treat a serious condition called **ADA-SCID** (*Adenosine Deaminase-Severe Combined Immune Deficiency*). With this condition the immune system does not work properly to defend the body against infections. People with ADA-SCID cannot produce enough of an enzyme called *adenosine deaminase (ADA)* because the gene to make it is faulty.

Strimvelis is used to treat ADA-SCID when there is no suitable match from a family member to donate stem cells from their bone marrow for a transplant.

Strimvelis is made specially for each patient, using the patient's own bone marrow cells. It works by putting a new gene into stem cells in the bone marrow so they can make ADA.

Strimvelis is given by a drip *(infusion)* into a vein *(intravenously)*. For more information on what happens before and during treatment, see section 3, *How Strimvelis is given*.

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 you (or to your child):

- are **allergic** to any of the ingredients of this medicine (*listed in section 6*)
- have or have had a type of **cancer** called *leukaemia* or *myelodysplasia*
- have tested positive for **HIV or some other infections** (your doctor will advise you about this)
- have already been treated with **gene therapy**

Warnings and precautions

Talk to your doctor or nurse before you (or your child) are given this medicine.

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 leukaemia. In clinical trials of gene therapy for other diseases (not ADA-SCID), some patients developed leukaemia or other cancers of the blood system. This has not been seen in any patient treated with Strimvelis; however, during long-term follow up your doctor has been advised to monitor you (or your child) for any signs of leukaemia.

After you (or your child) have been treated with Strimvelis, you or your child will not be able to donate blood, organs or tissues 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. There are several reasons why this might happen, for example:

- if there was a problem at the time the cells were taken for making the medicine
- if there were not enough of the right type of cells to make the medicine
- if the medicine got contaminated while it was being made
- if there was a delay in the medicine reaching the clinic where treatment is being carried out.

In such cases, the doctor will give you (or 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 you (or your child), the doctor will treat you as appropriate.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, if you think you may be pregnant or are planning to have a baby, tell your doctor before you are given this medicine. Strimvelis should not be given to you if you are pregnant. If it is possible that you could become pregnant, you must use a barrier contraceptive (such as condoms) during treatment and for at least 6 months afterwards.

You should not be given Strimvelis if you are breast-feeding. It is not known whether the ingredients of Strimvelis can pass into breast milk.

Strimvelis contains sodium
This medicine contains approximately 3.5 mg sodium per millilitre. This should be taken into consideration by patients on a controlled sodium diet.

3. How Strimvelis is given

Strimvelis is given by a drip *(infusion)* into a vein *(intravenously)*. It can only 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.

Strimvelis can only be made if the doctor can collect enough of the right kind of cells from the patient's own bone marrow.

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

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

- the **backup sample**, at least 3 weeks before. It will be stored, to be given to the patient as replacement stem cells if Strimvelis cannot be given or does not work *(see 'When Strimvelis treatment cannot be completed' in section 2)*
- the **treatment sample**, 4 to 5 days before. It will be used to make the Strimvelis, by putting 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 four times a day for two days (total of 8 doses)	to make the bone marrow ready for Strimvelis
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 ones marked * may be related to busulfan.

Very common side effects

These 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*
- blood test results positive for *antinuclear antibody and smooth muscle antibody*

If you have any questions about symptoms or side effects, or if any symptoms concern you

→ **Talk to your doctor or nurse.**

Common side effects

These may affect **up to 1 in 10 people**. They are all caused by the immune system becoming over-active and attacking the body's own tissues.

- red or purple dots on the skin, bleeding under the skin (*immune thrombocytopenic purpura*)
- inflamed thyroid gland (*autoimmune thyroiditis*)
- weakness and pain in the feet and hands (*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*

If you have any questions about symptoms or side effects, or if any symptoms concern you

→ **Talk to your doctor or nurse.**

Reporting of side effects
If you get 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

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 15-30°C.

Do not throw away any medicines via wastewater. 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 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 million $CD34^+$ 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

Orchard Therapeutics (Netherlands) BV
Prins Bernhardplein 200,
1097 JB Amsterdam,
the Netherlands

Manufacturer
MolMed SpA
58 Via Olgettina
20132
Milan
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: http://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:

Strimvelis is transported directly to the medical facility where the infusion will be administered. The infusion bag is 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 infusion bag(s) 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.

Following administration, a saline filled 50 ml syringe should be used to flush the bag through.

This medicinal product contains genetically-modified cells. Local biosafety guidelines applicable should be followed.

Strimvelis is not tested for transmissible infectious agents. Healthcare professionals handling Strimvelis should therefore take appropriate precautions to avoid potential transmission of infectious diseases.

Work surfaces and material which have potentially been in contact with Strimvelis must be decontaminated with appropriate disinfectant.

Any unused medicinal product or waste material should be disposed of in accordance with local biosafety requirements.