<Date>

Strimvelis® ▼ (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase [ADA] cDNA sequence): first case of lymphoid T cell leukaemia after insertional oncogenesis

Dear Healthcare professional,

Orchard Therapeutics (Netherlands) B.V. [hereafter Orchard], in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- **Lymphoid T cell leukemia has been reported in a patient with ADA-SCID 4.7 years after treatment with Strimvelis.**
- **This first case of a hematological malignancy following treatment with Strimvelis is considered to be due to insertional oncogenesis.**
- **Patients should be monitored long term, with at least annual visits for the first 11 years and then at 13- and 15-years post treatment with Strimvelis and include a complete blood count with differential, biochemistry and thyroid stimulating hormone.**

Background on the safety concern

Strimvelis is an autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with gamma-retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells. It 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.

A case of Lymphoid T cell leukaemia (T-cell type acute leukaemia) has been reported in a patient with ADA-SCID 4.7 years after treatment with Strimvelis in 2016. 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%.

At this moment, this is the only case of Lymphoid T cell leukaemia reported out of 33 patients with ADA-SCID treated with Strimvelis (frequency: 3%).
For comparison, the incidence of malignancies post-transplant for SCID patients (including ADA-SCID) has been reported as 25 out of 1,075 (2.3%) patients undergoing allogeneic HSCT between 1968 and 2003 and reported to the Center for International Blood and Marrow Transplant Research [Kamani, 2011].

The product information and Strimvelis educational programme materials are being

updated with the new information about the risk of malignancy due to insertional oncogenesis.

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>.

▼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.
When reporting possible adverse reactions, please include the individual patient lot number which can be found within the patient alert card.

Company contact point

For further information or medical inquiries, healthcare providers may contact medinfo@orchard-tx.com.

Communication Plan for Direct Healthcare Professional

DHPC COMMUNICATION PLAN	
Medicinal product/active substance	Strimvelis 1-10 x 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 with a concentration of 1-10 x 10^6 $CD34^+$ cells/mL
Marketing authorisation holder	Orchard Therapeutics (Netherlands) B.V. Prins Bernhardplein 200 1097 JB Amsterdam The Netherlands
Safety concern and purpose of the communication	Case of lymphoid T cell leukaemia due to insertional oncogenesis following treatment with Strimvelis
DHPC recipients	Physicians who have previously referred patients for treatment with Strimvelis
Member States where the DHPC will be distributed	Belgium, France, Germany, Italy, the Netherlands, Sweden.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	11 Feb 2021
DHPC and communication plan (in English) agreed by CAT	19 Feb 2021
DHPC and communication plan (in English) agreed by CHMP	25 Feb 2021
Submission of translated DHPCs to the national competent authorities for review	8 Mar 2021
Agreement of translations by national competent authorities	15 Mar 2021
Dissemination of DHPC	22 Mar 2021