Guide for Healthcare Professionals

IMPORTANT SAFETY INFORMATION FOR HEALTHCARE PROFESSIONALS

LIBMELDY® dispersion for infusion

(atidarsagene autotemcel)

The information contained in this guide is essential to ensure effective follow-up of metachromatic leukodystrophy (MLD) patients who have received gene therapy with Libmeldy, and appropriate monitoring and management of selected important risks associated with its use. Therefore, it is advised that you read this guide alongside the Summary of Product Characteristics (SPC) carefully before prescribing the product and subsequently following up patients.

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

About this guide

This guide includes important risk minimisation information for healthcare professionals who administer - and/or provide long-term follow-up of MLD patients post-treatment with - Libmeldy (an autologous $CD34^+$ cells enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* using a lentiviral vector expressing the human arylsulfatase A (ARSA) gene).

To manufacture Libmeldy, autologous $CD34^+$ HSPC are enriched from mobilised peripheral blood (mPB) and transduced with a lentiviral vector (LVV), which inserts one or more copies of the human ARSA gene into the cell genome, such that genetically modified cells become capable of expressing the functional ARSA enzyme.

Libmeldy is intended solely for autologous use and should under no circumstances be administered to other patients.

Malignancy risk due to insertional mutagenesis

In order to manufacture Libmeldy, a modified lentivirus is used to insert one or more functional copies of the ARSA gene into the patient stem cell genome. The process of inserting a new piece of DNA into the host cell genome may create a risk of oncogenic events such as leukemia or lymphoma. To date, no cases of malignant clonal expansion, malignancy or adverse events (AEs) indicative of oncogenic transformation have been reported in MLD patients. Also, so far there has been no evidence of aberrant clonal behaviour based on insertion site analysis in MLD patients treated with Libmeldy. Malignancy due to insertional mutagenesis remains a risk; therefore, it is important to monitor treated patients for signs and symptoms of oncogenic transformation, leukemia or lymphoma.

Advising parents & patients to monitor for signs and symptoms of leukemia or lymphoma

Parents or guardians, carers of children with MLD treated with Libmeldy, and when old enough, patients treated during childhood, must be advised about monitoring for symptoms and signs of leukemia or lymphoma (for example, breathlessness, clinical pallor, fevers, night sweats, swollen lymph nodes, easy bleeding/petechiae, frequent infections, fatigue), and should contact the patient's doctor immediately if they develop any of the symptoms described above.

Regular clinical monitoring is recommended

Complete blood count with red blood cell indices, white blood cell count differential, platelet count, and a routine biochemistry screen should be performed on a regular basis as per local clinical guidelines. These can be followed by a more detailed analysis if indicated, for example blood smear/film or cytogenetic testing. If leukaemia or lymphoma is detected in any patient who received Libmeldy, blood samples should be collected for integration site analysis.

If symptoms, signs or laboratory findings suggest oncogenic transformation, leukemia or lymphoma, they should be discussed with the patient (parent, guardian). Additionally, report these signs and findings, as well as any suspected adverse reactions involving Libmeldy, using the contact details provided at the end of this guide.

Delayed Platelet Engraftment

There have been cases of delayed platelet engraftment in a small number of patients treated with Libmeldy. This was not correlated with an increased incidence of bleeding, but remains an important risk.

Monitoring

Platelets counts should be monitored according to medical judgment until engraftment of these cells and recovery is achieved.

Management

Following myeloablative conditioning and treatment with Libmeldy, supportive transfusion of platelets should be given according to medical judgement and institutional practice.

Anti-ARSA Antibodies

The development of anti-ARSA antibodies (AAA) is a potential risk following treatment with Libmeldy. Monitoring for AAA prior to treatment and following treatment with Libmeldy is therefore recommended as described below (See also SPC section 4.4 for further information).

Monitoring

Monitoring of AAA is recommended at the following timepoints:

- Prior to treatment
- Post treatment: 1-2 months after gene therapy, 6 months, 1 year, 3 years, 5 years, 7 years, 9 years, 12 years, 15 years post treatment.

In case of disease onset or significant disease progression, additional AAA monitoring is also recommended.

Management

If the presence of AAA is confirmed (i.e. upon second/repeat test), a short treatment with rituximab can be considered, at the discretion of the treating physician, taking into consideration the AAA titers identified, clinical manifestations of the disease (neurological symptoms, delayed milestones) or other autoimmune manifestations for which there is an indication for a B-cell depletion treatment.

Patients in whom AAA are cleared following a course of rituximab should continue to be regularly monitored for the presence of antibodies for at least one year.

Engraftment failure

Failure of neutrophil engraftment is a short-term but potentially important risk, defined as failure to reach an absolute neutrophil count (ANC) >500 cells/µL associated with no evidence of bone marrow recovery (i.e. hypocellular marrow) by day 60 after myeloablative conditioning and Libmeldy infusion. In clinical trials, hematological recovery after conditioning with busulfan was typically seen four to five weeks from the day of Libmeldy infusion and none of the subjects reported engraftment failure. Patients should be monitored for signs and symptoms of cytopenia for at least 6 weeks after infusion.

Monitoring

Red blood cells and platelets counts should be monitored according to medical judgment until engraftment of these cells and recovery are achieved. Supportive transfusion of red cells and platelets should be given according to medical judgement and institutional practice. Blood cell count determination and other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise.

Management

If cytopenia persists beyond seven to eight weeks, despite the use of granulocyte mobilizing agents, the non-transduced back-up stem cells should be infused. If cytopenia persists despite infusion of non-transduced back-up stem cells, alternative treatments should be considered.

Rapidly progressive phase of the disease

Treatment with Libmeldy should be performed before the disease enters its rapidly progressive phase. Eligibility for treatment with Libmeldy should initially be assessed by the treating physician via full neurological examination, motor function assessment and neurocognitive assessment, as appropriate for the patients' age.

Prior to the commencement of cellular harvest, and prior to the commencement of conditioning, the treating physician should ensure that autologous HSPC gene therapy administration remains clinically appropriate for the patient, and that treatment with Libmeldy is still indicated.

Important points to discuss with patients and/or parents/carers

Please make sure that patients and/or parents/carers understand:

- The potential risks of a treatment with Libmeldy
- The signs of any malignancy, such as leukemia/lymphoma and what action to take
- The content of the patient and parent/carer guide and the patient alert card
- The need to carry the patient alert card and to show it to any healthcare professional
- The importance of regular monitoring and long term follow-up

Contact details for reporting suspected adverse reactions for Libmeldy

Report any suspected adverse reactions via the National Pharmacovigilance Centre (NPC) at Saudi Food and Drug Authority (SFDA) Call Center: 19999, E-mail: npc.drug@sfda.gov.sa, Website: https://ade.sfda.gov.sa/.
Also report any suspected adverse reactions involving Libmeldy to Orchard Therapeutics by email to drugsafety@orchard-tx.com and Cigalah by email to drug-safety@cigalah.com.sa.

When reporting possible adverse reactions, include the medicinal product lot number found on the patient alert card and Lot Information Sheet.