Package leaflet: Information for the patient or carer

Libmeldy 2-10 × 10^6 cells/mL dispersion for infusion
atidarsagene autotemcel

▼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 you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or nurse.
- Your child's doctor or nurse will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when your child sees them or if your child goes to hospital.
- 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.

What is in this leaflet

1. What Libmeldy is and what it is used for
2. What you need to know before your child is given Libmeldy
3. How Libmeldy is given
4. Possible side effects
   Side effects of the conditioning medicine
   Side effects of Libmeldy
5. How to store Libmeldy
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1. What Libmeldy is and what it is used for

What Libmeldy is

Libmeldy is a type of medicine called **gene therapy**. It is made specially for your child from your child's own blood cells.

What Libmeldy is used for

Libmeldy is used to treat a serious condition called metachromatic leukodystrophy (MLD):
- in children with the 'late infantile' or 'early juvenile' forms of the disease who have not yet developed any signs or symptoms,
- in children with the 'early juvenile' form of the disease who have started developing symptoms but whose symptoms are not yet worsening rapidly.

People with MLD have a fault in the gene to make an enzyme called arylsulfatase A (ARSA). This leads to a build-up of substances called *sulfatides* in the brain and nervous system, causing damage to the nervous system and progressive loss of physical skills and, later, mental ability, ultimately leading to death.

How does Libmeldy work?

Cells called *stem cells* are collected from your child's blood. They are then modified in a laboratory to insert a working gene for making ARSA. When your child is given Libmeldy, which is made up of

these modified cells, the cells will start making ARSA to break down the sulfatides in the nerve cells and other cells of your child's body. This is expected to slow down the progression of the disease and improve your child's quality of life.

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

If you have any questions about how Libmeldy works or why this medicine has been prescribed to your child, ask your child's doctor.

2. What you need to know before your child is given Libmeldy

Your child must not be given Libmeldy:

- if your child is allergic to any of the ingredients of this medicine (listed in section 6). If you think your child may be allergic, ask your doctor for advice.
- if your child has previously had gene therapy made from his/her blood stem cells.
- if your child is allergic to - or if your doctor thinks your child would get unacceptable side effects from - any of the ingredients in the medicines your child will be given before treatment with Libmeldy (see section 3).

Warnings and precautions

Talk to your doctor before your child is given Libmeldy.

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

- Libmeldy is made from your child's own stem cells and should only be given to your child.

Before the treatment with Libmeldy

- Evaluation of your child by their doctor to confirm that they have MLD and assess for symptoms and effects of their disease will take place before decision to use Libmeldy is made. Your child may not be showing any physical signs of the disease at the time of initial evaluation.
  If your child's MLD has progressed and has worsened before the initiation of the treatment, their doctor may determine that their disease has reached a 'rapidly progressive phase'. If this happens, your child may not gain benefit from the treatment and your child's doctor may decide not to give Libmeldy.

- Your child may be given medicines known as **mobilisation medicine** and **conditioning medicine** (see sections 3 and 4 for more information on these medicines, including possible side effects).

- 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.

- Libmeldy is tested for the presence of infectious microbes before it is administered to your child. There is a small risk of infection. Your child's doctors and nurses will monitor them throughout the infusion for signs of infection and provide treatment if needed.

- The doctor will check your child's thyroid gland. The thyroid gland is in the neck and it makes hormones that are important to help the body function normally. It will also be monitored after treatment if needed.

After the treatment with Libmeldy

- After the treatment, your child may be asked to enrol in a **follow up study** for up to 15 years to better understand the long-term effects of Libmeldy.

- If your child requires a blood transfusion within the first 3 months after they have received Libmeldy, blood products should be irradiated. This means the white blood cells, called lymphocytes, have been reduced to minimise the risk of a reaction to the transfusion. The doctor will monitor your child for any blood transfusion reaction.

- Your child's blood cells will be low for a period of time after the treatment with Libmeldy. This affects infection fighting blood cells called neutrophils that can be measured with a simple blood test. If your child's neutrophils are still low after 60 days, this may be called 'engraftment failure'. In such case, your child's doctor may decide to return the previously collected rescue cells to your child (see section 3). The rescue cells do not have the working ARSA gene added to them and will not produce the ARSA enzyme.

- After receiving the conditioning medicine, your child may have a low number of platelets in their blood. This means that your child's blood may not be able to clot normally and your child may be prone to bleeding for some time after the treatment. The doctor will monitor your child's platelet count with simple blood tests and provide your child with treatment if required. This may include a transfusion of platelets to help increase their platelet count.

- Metabolic acidosis may occur. It is a condition where the level of acid in the blood rises. There can be many different reasons for this, and the condition is more common in patients with MLD. Symptoms of metabolic acidosis include feeling breathless, rapid breathing, nausea (feeling sick) and vomiting. The doctor will monitor your child for signs and symptoms of metabolic acidosis.

- Inserting a new gene into the stem cells could theoretically cause blood cancers (leukaemia and lymphoma). After the treatment, your doctor will monitor your child for any signs of leukaemia or lymphoma.

- During the clinical studies, some patients developed antibodies to the ARSA enzyme, called anti-ARSA antibodies (see side effects of Libmeldy in section 4). This resolved on its own or after treatment with adapted medicines. Your child's doctor will monitor their blood for anti-ARSA antibodies and give treatment if needed.

- After your child has received Libmeldy, they will be monitored with regular blood tests. This will include measurement of antibodies, known as immunoglobulins, in their blood. If their level is low, your child may require immunoglobulin replacement therapy. Your child's doctor will discuss this with you if needed.

- Libmeldy is prepared using parts of the human immunodeficiency virus (HIV), which have been altered so that they cannot cause infection. The altered virus is used to insert the ARSA gene into your child's stem cells. Although this medicine will not give HIV infection to your child, having Libmeldy in their blood may cause a false positive HIV test result with some commercial tests (so-called "PCR-based tests") that recognise a piece of HIV used to make Libmeldy. If your child tests positive for HIV after Libmeldy treatment, please contact your child's doctor or nurse.

- After a treatment with Libmeldy, your child will not be able to donate blood, organs, tissues or cells. This is because Libmeldy is a gene therapy product.

Before your child is given Libmeldy the doctor will:

- Check your child's lungs, heart, kidney, liver, as well as blood pressure.
- Look for signs of infection; any infection will be treated before your child is given Libmeldy.
- Check for hepatitis B, hepatitis C, human T-cell lymphotropic virus (HTLV), HIV or mycoplasma infection.
- Check if your child had a vaccination in the previous 6 weeks or if one is planned in the next few months.

When Libmeldy treatment cannot be completed

Before receiving Libmeldy your child will be given a conditioning medicine to remove cells from their bone marrow.

If Libmeldy cannot be given after your child has had the conditioning medicine, or if the modified stem cells do not take hold *(engraft)* in your child's body, the doctor may decide to return the previously collected rescue cells to your child by infusion (see also section 3, *How Libmeldy is given*). The rescue cells do not have the working ARSA gene added to them and will not produce the ARSA enzyme. For more details, please contact your child's doctor.

Other medicines and Libmeldy

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

- Your child should not take any **medicines for HIV infection** from at least one month before your child is given the mobilisation medicines, until at least 7 days after Libmeldy infusion (see also section 3, *How Libmeldy is made and given*).
- Your child must not be given vaccines called **live vaccines** for 6 weeks before they are given the conditioning medicine to prepare for Libmeldy treatment, nor after treatment while your child's immune system (the body's defence system) is recovering.

Libmeldy contains sodium and dimethylsulfoxide (DMSO)

This medicine contains 35-560 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 2 to 28% of recommended maximum daily dietary intake of sodium for an adult.

If your child has not previously come into contact with DMSO (a substance used to preserve frozen cells), the doctor or nurse should watch your child closely for any reactions during the infusion and every hour, for 3 hours, after the infusion.

3. How Libmeldy is given

Since Libmeldy is made from your child's own stem cells, your child's blood will be drawn from a vein and collected to prepare the medicine about 2 months before treatment.

- Your child will first be given a mobilisation medicine to move the blood stem cells from your child's bone marrow into their blood stream.
- The blood stem cells can then be collected by a machine that separates blood components *(apheresis machine)*. It may take more than 1 day to collect enough blood stem cells to make Libmeldy.

The stem cells collected from the blood will be divided into:

- The **treatment sample,** which will be sent away to make Libmeldy, by inserting a working copy of the ARSA gene into the stem cells in the sample.

- The **backup sample,** which will be frozen and stored, to be given to your child as replacement stem cells if Libmeldy cannot be given or does not work (see *'When Libmeldy treatment cannot be completed'* in section 2). Of note, the back-up cells may alternatively be collected from your child's bone marrow. In such a case, your child will be given medicines to relax and prevent pain or make them unconscious before the procedure. The doctor will collect your child's bone marrow using a special syringe.

How your child is given Libmeldy
- Libmeldy will be given to your child in a qualified treatment centre and by doctors trained in using this type of medicine.
- The doctors will check that the Libmeldy infusion bags are all identified as being made from your child's own sample.
- Libmeldy is a one-time treatment. It will not be given to your child again.

When	What happens	Why
About 2 months before Libmeldy infusion	Mobilisation medicine is given	To move the blood stem cells from your child's bone marrow into the blood stream.
About 2 months before Libmeldy infusion	Blood is collected	To make Libmeldy and to serve as replacement cells if needed.
5 days before Libmeldy infusion	A conditioning medicine is given for 3–4 days in a hospital	To prepare your child's bone marrow for treatment by destroying cells in the bone marrow so they can be replaced with the modified cells in Libmeldy.
15 to 30 minutes before Libmeldy infusion	A medicine called an antihistamine may be given	To help prevent an allergic reaction to the infusion
Start of Libmeldy treatment	Libmeldy is given by a drip (infusion) into a vein. This will be in a hospital and will take about 30 minutes for each infusion bag. The number of bags will vary by patient.	To add stem cells containing the ARSA gene into your child's bone marrow.
After Libmeldy treatment	Your child will remain in the hospital for about 4–12 weeks	To recover and be monitored to check if your child's treatment is working and help if they have any side effects until the doctor is satisfied that it is safe for your child to leave the hospital.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

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

Some side effects are related to the conditioning medicine used to prepare your child's bone marrow for treatment with Libmeldy.

Talk with your child's doctor about side effects of the conditioning medicine. You may also read the package leaflets for that medicine.

Side effects of the conditioning medicine

➔ **Tell the doctor or nurse immediately** if your child gets any of the following side effects after receiving the conditioning medicine. They usually happen between the first few days and several weeks after receiving the conditioning medicine but can also develop much later.

Very common side effects (may affect more than 1 in 10 people)

- blood tests showing low level of white blood cells without or with a fever
- metabolic acidosis, a condition where the acid levels in the blood are raised
- inflammation and sores of the mouth and lips
- being sick (*vomiting*)
- enlarged liver
- pain in the right upper abdomen (belly) under the ribs, yellowing of eyes or skin, rapid weight gain, swelling of arms, legs and abdomen, and trouble breathing. These may be signs of a serious liver condition called *veno-occlusive disease*
- loss of function or decreased function of ovaries

Common side effects (may affect up to 1 in 10 people)

- abnormal bleeding or bruising - may be caused by low level of blood platelets, reducing the ability of blood to clot
- infections which may make your child feel hot (feverish), chilly or sweaty
- chest infection (*pneumonia*)
- infection of the organs involved in excretion of urine (such as the bladder and urinary tract)
- low level of red blood cells (*anaemia*)
- excess fluid in body
- build-up of fluid in the abdomen
- trouble sleeping
- headache
- nosebleeds
- pain in the mouth and throat
- diarrhoea
- bleeding in the digestive tract
- feeling sick (*nausea*)
- increase in liver enzymes (transaminases and aminotransferases) seen in blood tests
- itchy skin
- back pain
- bone pain
- decreased urine production
- fever
- positive test for Aspergillus (lung disease caused by fungus)

Side effects of Libmeldy

The following side effects have been reported with Libmeldy.

Very common side effects (may affect more than 1 in 10 people)

- positive test for antibodies against ARSA. Antibodies are the body's natural defence against anything that the body thinks is foreign.

Reporting of side effects
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. You can also report side effects directly via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Libmeldy

The following information is intended for doctors only.

As this medicine will be given in a hospital, the hospital is responsible for the correct storage of the medicine before and during its use, as well as for its correct disposal.

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

Do not use this medicine after the expiry date which is stated on the outer container and infusion bag labels.

Do not use this medicine if you notice that the infusion bag is damaged or leaking.

Store at < -130 °C for up to 6 months. Do not thaw the product until it is ready to be used. Once thawed, keep at room temperature (20 °C-25 °C) and use within 2 hours. Do not refreeze.

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.

6. Contents of the pack and other information

What Libmeldy contains

- The active substance of Libmeldy consists of your child's own stem cells that contain working copies of the ARSA gene. The concentration per bag is 2–10 × 10^6 cells per millilitre.

- The other ingredients are a solution used to preserve frozen cells and sodium chloride (*see section 2, Libmeldy contains sodium*).

This medicine contains genetically modified human blood cells.

What Libmeldy looks like and contents of the pack

Libmeldy is a clear to slightly cloudy, colourless to yellow or pink dispersion of cells that is supplied in one or more clear infusion bags, each packed in a pouch inside a closed metal container.

Your child's name and date of birth, as well as coded information identifying your child as the patient, are printed onto each infusion bag and each metal container.

Marketing Authorisation Holder

Orchard Therapeutics (Europe) Limited
245 Hammersmith Road
London
W6 8PW
United Kingdom

Manufacturer

AGC Biologics SpA
Zambon Scientific Park
Via Meucci 3
200091 Bresso (MI)
Italy

AGC Biologics SpA
Via Olgettina 58
20132
Milan
Italy

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The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Libmeldy.

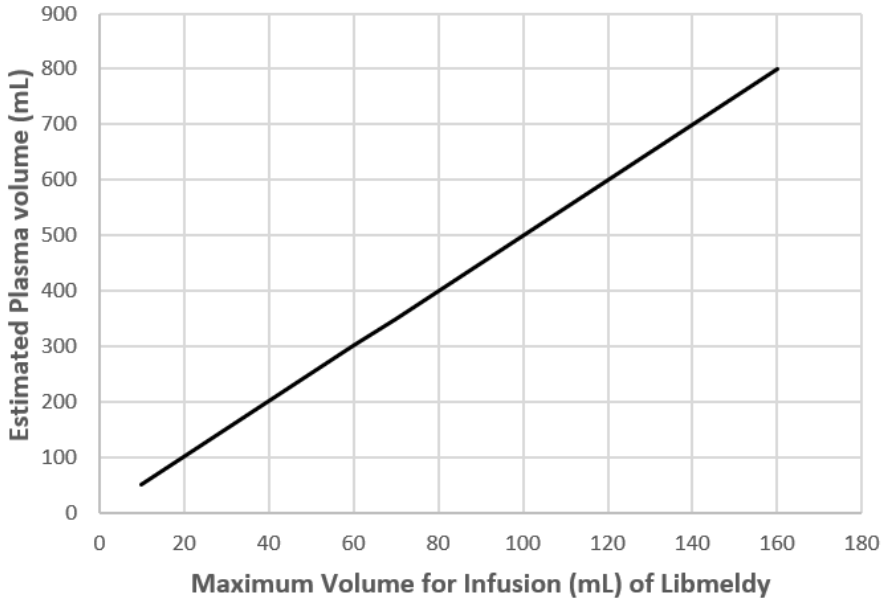
Precautions to be taken before handling or administering the medicinal product

- This medicinal product contains human blood cells. Healthcare professionals handling Libmeldy must take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.
- Libmeldy must remain at <-130 °C at all times, until the content of the bag is thawed for infusion.

Defining the dose to be administered

- The dose to be infused and number of Libmeldy infusion bags to be used should be defined based on the total number of $CD34^+$ cells supplied indicated on the Lot Information Sheet (i.e. the 'supplied dose', calculated based on patient's weight at time of cell harvest). The dose of Libmeldy to be administered should also take into account the patient's weight at the time of treatment, and the fact that any bag used should be administered in its entirety.
- Careful consideration must be given to the volume of infusion in relation to age and weight of the patient. When the dose of Libmeldy to be infused represents more than one bag, it should be ensured prior to infusion that the volume of medicinal product to be infused is compatible with the recommended limit of DMSO, i.e. the total volume of DMSO administered should remain <1% of the patient's estimated plasma volume. Therefore, the maximum volume of Libmeldy to be administered should remain < 20% of the patient's estimated plasma volume.
- The following graph is provided as a reference in order to determine the maximum volume of Libmeldy which can be infused to a patient based on their estimated plasma volume.

Guidance on DMSO safety limit: the maximum volume of Libmeldy to be administered should remain < 20% of the patient's estimated plasma volume.



Preparation prior to administration

- A patient may have multiple infusion bags. Each infusion bag is provided inside an overwrap bag, which is contained in a metal cassette.
- The overwrapped infusion bag(s) must be kept inside the metal cassette(s) in the vapour phase of liquid nitrogen at < -130 °C until ready to thaw and infuse.
- Account for all infusion bags and confirm each infusion bag is within the expiry date using the accompanying Lot Information Sheet.
- Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be available to prime the tubing prior to infusion, and to flush the infusion bag and tubing after infusion.

Checking prior to thawing

- Do not remove the metal cassette from cryogenic storage and thaw Libmeldy until the patient is ready to be infused. The timing of thaw of the infusion bag(s) containing Libmeldy and of the infusion should be coordinated. Confirm the infusion time in advance and adjust the start time for thaw so that Libmeldy is available for infusion when the recipient is ready.
- Open the metal cassette and inspect the overwrap bag and infusion bag for any breaches of integrity before thawing. If an infusion bag is compromised, follow the local guidelines on handling of waste of human-derived material and contact Orchard Therapeutics immediately.
- Prior to thawing Libmeldy, it must be verified that the patient identity matches the unique patient information reported on the packaging labels and on the accompanying Lot Information Sheet. Libmeldy is intended solely for autologous use. Do not thaw or infuse Libmeldy if the information on the patient-specific label on the infusion bag does not match the intended patient.

Thawing

- After careful removal from the metal cassette, thaw the infusion bag in its sealed overwrap bag at 37 °C in a controlled thawing device until there is no visible ice in the infusion bag.
- Once thawing is complete, the bag should be removed immediately from the thawing device.
- The overwrap bag should be carefully opened to remove the infusion bag which should be kept at room temperature (20 °C-25 °C) until infusion.

- Gently massage the infusion bag to resuspend the cells. The content of the infusion bag should be inspected for any remaining visible cellular aggregates. Small clumps of cellular material should disperse with gentle manual mixing. Do not shake the bag.
- The infusion bag should not be washed, spun down, sampled and/or resuspended in new media prior to infusion.
- Libmeldy should not be irradiated as irradiation could lead to inactivation of the product.
- If more than one infusion bag is provided for the patient treatment dose, the next bag should only be thawed after the content of the preceding bag has been fully infused.

Administration

- Libmeldy should be administered as an intravenous infusion via a central venous catheter, per the qualified treatment centre's standard procedures for cell therapy products.
- The recommended administration set consists of a blood transfusion set equipped with a 200µm filter.
- Each bag should be infused by gravity within 2 hours of thaw, including any interruption during the infusion, to maintain maximum product viability.
- The maximum infusion rate is 5 mL/kg/h, and the content of each bag should be infused within approximately 30 minutes.
- When more than one bag of Libmeldy is needed, only one bag of product should be infused per hour.
- Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be monitored for up to 3 hours following the infusion.
- At the end of the infusion, flush all Libmeldy remaining in the infusion bag and any associated tubing with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that as many cells as possible are infused into the patient. Careful consideration must be given to the volume of infusion in relation to the age and weight of the patient.

Measures to take in case of accidental exposure

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

Precautions to be taken for the disposal of the medicinal product

- Unused medicinal products and all material that have been in contact with Libmeldy (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.