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UNLOCK THE FUTURE

Actor portrayal. MLD is a recessive inherited disease.

for children with early onset* metachromatic leukodystrophy (MLD)

What is LENMELDY?

LENMELDY is a one-time gene therapy developed to treat children with pre-symptomatic late infantile, pre-symptomatic early juvenile and early symptomatic early juvenile, referred to as early-onset, metachromatic leukodystrophy (MLD). MLD is caused by a defect in the arylsulfatase A (*ARSA*) gene, which causes the body to produce reduced or no ARSA enzyme. LENMELDY is made specifically for each child, using the child's own blood stem cells, and adding functional copies of the *ARSA* gene to their cells. This may allow the child to produce sufficient ARSA enzyme to stop or slow the progression of MLD symptoms.

*See full indication.

Please see Important Safety Information throughout and full Prescribing Information.

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About the information in this brochure

This brochure is intended to provide information to help you and your family understand and navigate the diagnosis and treatment of early onset* metachromatic leukodystrophy (MLD). It includes details on the signs and symptoms of MLD, helpful information about treatment, and how to reach out for support along the way.

*See full indication.

Important Safety Information

What is the most important information I should know about LENMELDY?

The most common side effects you should be aware of with LENMELDY are:

- Fever
- Swelling or sores inside the mouth
- Reduction in blood clotting ability and possibility of excess bleeding due to a lower level of platelets
- Increased risk of infection due to decreased level of white blood cells (WBC)

GLOSSARY

If you see terms in **bold** throughout this brochure, you can refer to this helpful glossary for the definition.

ARSA gene
The gene responsible for making the arylsulfatase A (ARSA) enzyme, which works to break down substances called sulfatides.

Blood stem cells or hematopoietic stem cells (HSCs)
Cells capable of producing copies of themselves and making blood cells of all types, including white blood cells, red blood cells, and platelets.

Chemotherapy
Medication that kills cells in the body. In gene therapy, chemotherapy destroys cells in the bone marrow, making room for the new gene-corrected cells.

Enzyme
Complex proteins that cause a specific chemical change. Enzymes are needed for all body functions and can be found in every organ and cell in the body.

Genes
Small sections of DNA that contain the instructions for individual characteristics, like eye and hair color, and how to make proteins, which are the functional building blocks of the cell.

Gene therapy
A technique that aims to use genes to treat disease.

Myelin sheath
A protective fatty layer that surrounds the nerves in the brain (central nervous system) and in the nerves in your body (peripheral nervous system).

Variant
A change in the structure of a gene or group of genes. Such changes can be passed on from parent to child. Many variants cause no harm, but others can cause genetic disorders.

WHAT ARE GENES?

Genes are small sections of DNA. Every person has 2 copies of each gene, 1 passed down—or inherited—from each parent.

Genes act as instructions to make proteins, the functional building blocks of the cell. Proteins are responsible for making sure that the cells in the body function properly. Much like a cookbook contains a recipe for a cake, a gene contains the instructions to make a protein.

A genetic **variant** is a change in the structure of a gene or group of genes. Many variants cause no harm, but others can cause genetic disorders, such as MLD.

HEMATOPOIETIC STEM CELLS

A person's body contains **blood stem cells**, otherwise known as **hematopoietic stem cells (HSCs)**. HSCs are made in the bone marrow, which is the spongy tissue found in the center of most bones.

Stem cells can produce copies of themselves and create specialized blood cells of all types, including white blood cells, red blood cells, and platelets. The body uses these stem cells to make new cells when it needs them throughout a person's life.

WHAT IS MLD?

MLD (metachromatic leukodystrophy) is a rare, inherited disease. In people with MLD, the lack of an **enzyme** called ARSA can destroy the protective layer of the nerves known as the **myelin sheath**. This damages the nerves and causes worsening motor issues, such as weakness and trouble walking, and a decline in brain function. MLD is ultimately fatal.

That's why early diagnosis is so important.

There are multiple types of MLD that occur during various stages of childhood. When this disease occurs before a child is 30 months old, it is known as late infantile MLD. When it occurs after 30 months and before the age of 7, it is known as early juvenile MLD.

HOW MLD MAY AFFECT YOUR CHILD

Early signs of MLD

The most common early signs of late infantile and early juvenile MLD reported by caregivers are motor symptoms and cognitive symptoms.

These may appear as an increasing difficulty with moving, talking, swallowing, or eating. The age when children start showing symptoms may vary depending on the form of MLD and the parts of the brain that are affected.

It is important to note that patients do not need to have both early motor and cognitive symptoms to be diagnosed with MLD.

		LATE INFANTILE MLD ≤30 months	EARLY JUVENILE MLD 30 months to 7 years
EARLY SYMPTOMS			
Motor	Loss of muscle tone	✓	✓
	Weakness	✓	✓
	Frequent falls	✓	✓
	Unsteady/sluggish gait	✓	✓
	Loss of balance, unstable walking	✓	✓
Overall development	Missing milestones	✓	✓
	General regression	✓	✓
Cognitive	Cognitive decline (school performance)		✓
	Speech difficulties		✓
	Behavioral changes		✓

Over half of children affected by MLD show symptoms before their third birthday

GENE THERAPY WITH LENMELDY

LENMELDY is a **blood stem cell**-based **gene therapy** for the treatment of:

Pre-symptomatic late infantile (PSLI) MLD in infants under 30 months old who have not yet shown symptoms

Pre-symptomatic early juvenile (PSEJ) MLD in young children between 30 months and 7 years old who have not yet shown symptoms

Early symptomatic early juvenile (ESEJ) MLD in young children between 30 months and 7 years old with early-stage symptoms

LENMELDY uses the child's own blood stem cells to correct MLD. The cells are first collected from the child in a specialized clinic, then the cells are sent to a gene therapy lab where they insert a working copy of the ***ARSA* gene** into the cells. Those cells can then be returned to the child in a specially trained hospital.

ELIGIBILITY ASSESSMENT

MLD specialists at your Qualified Treatment Center (QTC) will perform a series of tests to determine whether or not your child is medically eligible for treatment with LENMELDY.

Your child will receive treatment with LENMELDY at a QTC. These QTCs are highly qualified facilities that have been trained to administer LENMELDY. Your doctor will provide a referral to a QTC.

HOW WILL YOUR CHILD RECEIVE LENMELDY?

As part of the LENMELDY treatment regimen, your doctors will prescribe additional medications to prepare your child's body for LENMELDY. This will include administration of **chemotherapy**. It is important to talk to your doctor about your child's therapy to be fully informed of all risks and benefits of treatment.

WHAT OTHER MEDICINES WILL MY CHILD NEED?

Your doctors will give your child other medicines, including chemotherapy, as part of treatment with LENMELDY. It is important to talk to your doctors about the risks and benefits of all medicines involved in your child's treatment.

STEP 1

AT THE QTC: 5-7 DAYS

LENMELDY IS MADE SPECIFICALLY FOR EACH CHILD USING THEIR OWN BLOOD STEM CELLS

Your doctor will collect your child's blood stem cells through a process called mobilization and apheresis (A-feh-REE-sis). The apheresis process takes 1 to 3 days to collect enough blood stem cells to make LENMELDY.

STEP 2

HOME 40-42 DAYS

THE STEM CELLS ARE THEN SENT TO A DRUG MANUFACTURING LAB WHERE THEY ARE USED TO MAKE LENMELDY

It takes approximately 6 to 8 weeks from the time cells are collected to manufacture and test LENMELDY before it is shipped back to the QTC (timing may vary). Your child does not have to be in the QTC while this is done.

STEP 3

AT THE QTC: 3-5 DAYS

CHEMOTHERAPY HELPS PREPARE BONE MARROW FOR TREATMENT

Before your child receives LENMELDY, your doctor will give them chemotherapy for a few days to prepare their bone marrow to accept the new cells. Your child will be readmitted to a qualified treatment center (QTC) for this step and remain in the QTC for the LENMELDY infusion.

STEP 4

AT THE QTC: 4-12 WEEKS

LENMELDY IS GIVEN BY INTRAVENOUS INFUSION (INJECTED INTO THE VEIN)

Your child may receive more than one bag of LENMELDY. Each bag is infused in about 30 minutes.

After the infusion, your child will stay in the QTC for approximately 4 to 12 weeks so the doctors can closely monitor recovery. Your doctors will decide when it is appropriate for your child to go home.

Please see Important Safety Information throughout and full Prescribing Information.

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AFTER TREATMENT WITH LENMELDY

37 children were evaluated for efficacy in clinical trials.

20 of the children had been diagnosed with PSLI MLD, 7 with PSEJ MLD, and 10 with ESEJ MLD.

Children with PSLI MLD

Survival

14 children treated with LENMELDY were alive and had reached the age of 6 years old, while 10 of the untreated children had passed away before the age of 6.

Severe motor impairment

- 17 children with PSLI MLD treated with LENMELDY were followed until at least the age of 5 years
- **At the age of 5 years, 100% of LENMELDY-treated PSLI children remained free of severe motor impairment** (loss of movement and loss of sitting without support). All of the untreated children experienced loss of movement and loss of sitting without support by the age of 5
- **12 children treated with LENMELDY who had reached the age of at least 5 years** (up to 13 years old) were able to walk independently at their last follow-up

Lower cognitive impairment

- Cognitive impairment can include difficulties with thinking and problem solving
- **19 of 20 children with PSLI MLD remained free of severe cognitive impairment** through last follow-up
- Most of the LENMELDY-treated PSLI children maintained normal cognition based on standard performance scores at last follow-up. The untreated children demonstrated severe cognitive impairment early in their disease

Important Safety Information (continued)

What is the most important information I should know about LENMELDY? (continued)

Call your doctor right away if the child has new or unusual bleeding, which may include any of these signs or symptoms:

- Severe headache
- Abnormal bruising
- Nosebleed
- Blood in urine, stool, or vomit
- Coughing up blood
- Unusual stomach or back pain

Please see Important Safety Information throughout and full Prescribing Information.

Children with PSEJ MLD

Motor function

In the trial, 7 children with PSEJ MLD were treated with LENMELDY.

At the time of last follow-up, 1 child had passed away from a stroke, and 3 children were too young to evaluate since symptoms may not show up until 7 years of age.

3 of the children with PSEJ MLD at last follow-up who were old enough to evaluate had normal gait and were walking without support (follow-up occurred at least 3 years post-treatment). Of the 2 untreated matched siblings, only 1 was able to walk without assistance.

Cognitive function

2 children were evaluated and had normal cognitive function approximately 5 to 7 years after being treated.

Children with ESEJ MLD

10 children with ESEJ MLD were studied

At last follow-up, 1 child could not be evaluated due to the progression of their disease, and 2 children had passed away from MLD. All 7 remaining children were evaluated for 2 to 9 years after LENMELDY treatment.

Of the remaining 7 children in the study, 6 children had normal cognitive function

5 children were able to sit, crawl, or roll by themselves, but were unable to walk without assistance.

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IMPORTANT SAFETY INFORMATION (continued)

What is the most important information I should know about LENMELDY? (continued)

The child may experience side effects with medicines administered as part of the LENMELDY treatment regimen. Your doctor may give other medicines to treat the side effects.

After treatment with LENMELDY, the child may experience low blood counts. This can put the child at greater risk for bleeding and/or infection. Your doctor will monitor the child and may provide other treatment until their blood counts return to safe levels.

Children treated with LENMELDY may experience serious or life-threatening infections, including infections of the bloodstream by bacteria or viruses. Most infections occur in the first 1 or 2 months after treatment with LENMELDY but can occur >1 year later. Tell your doctor right away if the child develops fever, chills, or any signs or symptoms of an infection.

Children treated with LENMELDY may experience Veno-Occlusive Disease (VOD), or blocking of veins to the liver, causing damage to the liver. Your doctor will monitor the child for signs and symptoms of VOD during the first month after LENMELDY infusion.

The child will need to be monitored annually, at a minimum, for at least 15 years. This is necessary to ensure there are no changes to their blood panel as there is a potential risk of blood cancer associated with this treatment; it should be noted that no such cases have been reported in clinical studies of LENMELDY.

If the child is diagnosed with cancer, have your doctor contact Orchard Therapeutics at 1-888-878-0185.

How will the child receive LENMELDY? (continued)

Treatment with chemotherapy is associated with several unique risk factors. One specific side effect involves fertility; after receiving chemotherapy, it may not be possible for the child to become pregnant or father a child. You should consider discussing options for fertility preservation with your doctor before treatment.

What should the child avoid after receiving LENMELDY?

- Do not donate blood, organs, tissues, or cells

What are additional possible or reasonably likely side effects of LENMELDY?

While receiving chemotherapy to prepare the child's body for LENMELDY:

- Chemotherapy is administered to prepare their bone marrow to accept LENMELDY. Chemotherapy is often associated with a variety of side effects, including:
  - Nausea
  - Vomiting
  - Decreased appetite
  - Constipation
  - Abdominal pain
  - Headache
  - Rash

Following treatment

- **Blood issues**
  Once the child has completed their treatment regimen, they may experience low blood counts. This may put them at greater risk of bleeding and/or infection.

  Until the child's blood counts (platelets, white blood cells, red blood cells) return to safe levels, they may be treated with blood and platelet transfusions and other medicines that prevent bleeding and infection by increasing blood counts.

  Most children's blood counts return to safe levels about one month after treatment with LENMELDY. However, some blood counts may not recover for >1 year.

- **Life-threatening infections**
  Treatment with LENMELDY may cause serious or life-threatening infections, including infections of the bloodstream by bacteria or viruses.

  Most infections occur in the first 1 or 2 months after treatment with LENMELDY but can occur >1 year later. *Tell your doctor right away if the child develops fever, chills, or any signs or symptoms of an infection.*

  LENMELDY *will not* give the child human immunodeficiency virus (HIV) infection. Treatment with LENMELDY may cause a false-positive HIV test result by some commercial tests. If the child needs an HIV test, talk with your doctor about the appropriate test to use.

- **Other issues**
  Inflamed and painful mouth (typically occurs during the first 2 months after LENMELDY), nausea, vomiting, decreased appetite, constipation, abdominal pain, diarrhea, headache, and new onset seizures may occur.

  Treatment with LENMELDY may cause brain inflammation. *Tell your doctor right away if the child develops weakness, decreased muscle tone, loss of mental clarity, vomiting, and swallowing difficulties.*

As always, tell your doctor right away if the child gets a fever, is feeling tired, or experiences easy bleeding or bruising.

It is important that the child has regular check-ups with your doctor, including at least annual blood tests, to detect any adverse effects and to confirm that LENMELDY is still working. Talk to your doctor about any concerns.

Please see the full Prescribing Information for LENMELDY.

These are not all the possible side effects of LENMELDY. Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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YOUR JOURNEY BEGINS WITH ORCHARD ASSIST

Orchard assist

Orchard Assist is here to help you navigate the services and support available to families embarking on gene therapy. With Orchard Assist, you can get help with questions regarding your insurance coverage, support, and treatment journey planning, as well as a dedicated representative supporting you along the way.

What you can expect from Orchard Assist

How health insurance works: Your representative will help your family with understanding what is covered, determining what your out-of-pocket expenses might be, and if travel and lodging are covered by your plan.

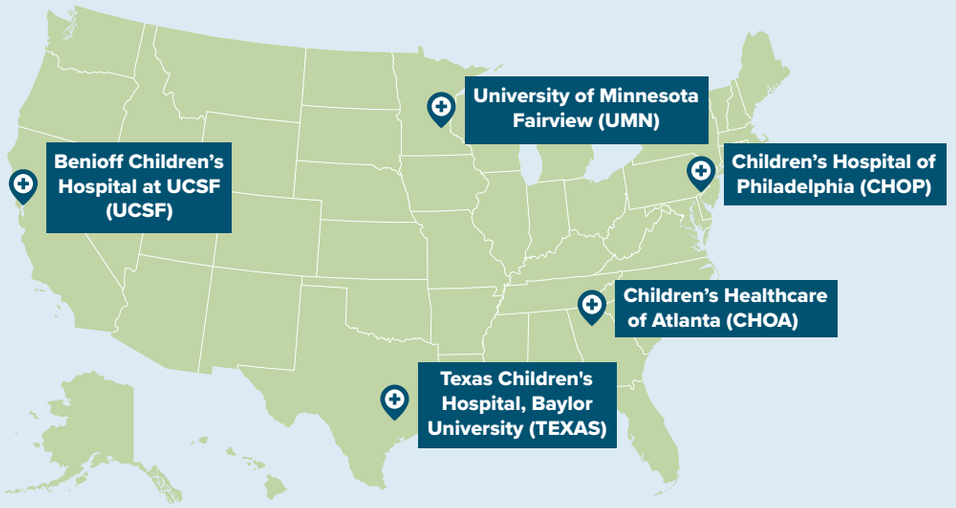
Benefits investigation and prior authorization: Your representative may help you understand what is covered for treatment.

Treatment journey planning: Everyone's treatment journey is different, and Orchard Assist is here to help you at every step of the way, before and after treatment.

Contact Orchard Assist today and speak to a representative.

TREATMENT CENTER LOCATIONS

Qualified Treatment Centers (QTCs) are medical centers that have been trained to administer Orchard Therapeutics gene therapy.*



*All treatment centers are currently awaiting final confirmation.

QTCs are independently owned and operated. Orchard Therapeutics does not have oversight over any QTC or the medical care they provide. Contact the QTC or Orchard Assist for additional information.

Inclusion of a QTC on this map does not represent an endorsement, referral, or recommendation from Orchard Therapeutics. It is the sole discretion of patients and their healthcare professional to determine which QTC may be the best fit for them.

Please note that the circumstances of coverage may vary based on the QTC. An Orchard Assist representative may be able to provide information about insurance coverage.

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TO LEARN MORE ABOUT GENE THERAPY WITH

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&

SUPPORT THROUGH

Orchard assist

VISIT LENMELDY.COM

It is important that you keep up with your child's checkups and talk with your child's doctors and care team about any concerns.

Please see Important Safety Information throughout and full Prescribing Information.

Orchard therapeutics

Date of preparation: April 2024 | US-002-2400036