INDICATION

KANUMA® is indicated for the treatment of people with a diagnosis of lysosomal acid lipase deficiency (LAL-D).

IMPORTANT SAFETY INFORMATION

Allergic Reaction

Life-threatening and severe allergic reactions may occur in people who receive KANUMA. These reactions may occur in people who are starting treatment with KANUMA or in people who have previously received KANUMA without having an allergic reaction.

Please see the Important Safety Information throughout and on page 11 and the accompanying full Prescribing Information for KANUMA® (sebelipase alfa).
STARTING TREATMENT WITH KANUMA® (sebelipase alfa)

You may have questions about starting your KANUMA treatment. Be sure to discuss your questions with your doctor. Use this brochure as a guide.

Inside, you will find

- Information about KANUMA (pages 4-5)
- What to expect before, during, and after your infusions (pages 6-7)
- Support for people with LAL-D (pages 8-9)

Talk to your doctor if you have questions about KANUMA or LAL-D. For additional support or questions about KANUMA or LAL-D, contact the OneSource™ patient support program at 1-888-765-4747. See page 8 for more details.

IMPORTANT SAFETY INFORMATION

Allergic Reaction (cont’d)

You should seek immediate medical care if any of these signs or symptoms that may be related to a severe allergic reaction occur:

- Rash such as hives; may also include itching
- Difficulty breathing, shortness of breath, tightness in the chest, and wheezing (noises while breathing)
- Dizziness or feeling faint
- Tingling and swelling around the mouth, in your throat, or eyes
- Fast heartbeat
- Very low blood pressure
- Sweating
- Loss of consciousness
- Flushing or temporary reddening of the skin (usually on the face)
- Agitation or irritability

Please see the Important Safety Information throughout and on page 11 and the accompanying full Prescribing Information for KANUMA® (sebelipase alfa).
ABOUT KANUMA® (sebelipase alfa)

What is KANUMA?
KANUMA is a prescription treatment for people with a diagnosis of Lysosomal Acid Lipase Deficiency (LAL-D).

What does KANUMA do?
Patients with LAL-D are born with a missing or dysfunctional enzyme that is important for your body. This enzyme, called lysosomal acid lipase (LAL), plays an important role in a key part of your body’s cells, called lysosomes, by breaking down fatty material. Buildup of fatty material can cause continuous damage that may affect the function of many organs throughout your body. KANUMA helps to replace the LAL enzyme that is missing or not working correctly.

How is KANUMA administered?
KANUMA is administered by intravenous (IV) infusion. An IV infusion is a way of delivering medicine directly into your bloodstream. KANUMA is given once every other week in children and adults, and once weekly in infants.

What is the recommended dosage of KANUMA?
For infants with rapidly progressive LAL-D presenting within the first 6 months of life, the recommended starting dosage of KANUMA is 1 mg/kg of body weight given by IV infusion once weekly. For infants under 6 months who do not respond to this dose, the doctor may increase the dosage to 3 mg/kg of body weight once weekly. For patients who do not respond to this dose, the doctor may further increase the dosage to 5 mg/kg once weekly.

For children and adults presenting with LAL-D, the recommended dosage of KANUMA is 1 mg/kg of body weight given by IV infusion once every other week. For patients who do not respond to this dose, the dosage may be increased to 3 mg/kg once every other week.

How long will my infusion last?
Your KANUMA® (sebelipase alfa) infusion will last at least 2 hours, though your doctor may decide to increase or decrease your infusion time.

Where will I go for my infusions?
Your doctor will talk with you about when and where your infusions will happen. They may be scheduled in his or her office, a hospital, or a specialized infusion center.

Do I need to get all of the infusions recommended by my doctor?
Yes. LAL-D is a genetic disease, which means that your body’s makeup does not allow it to produce a properly functioning LAL enzyme. KANUMA is intended to replace the LAL enzyme that does not work correctly or may be missing. Talk to your doctor about the importance of staying on treatment.

When will I know if KANUMA is working?
You may not feel KANUMA working. Your doctor will monitor your care and review the appropriate test results.

Does KANUMA have side effects?
In infants with rapidly progressive disease presenting within the first 6 months of life treated with KANUMA, the most common side effects are diarrhea, vomiting, fever, stuffy or runny nose, anemia (low red blood cells), cough, swelling of the nose and throat, and hives.

In pediatric and adult patients treated with KANUMA, the most common side effects are headache, fever, sore throat, swelling of the nose and throat, weakness, constipation, and nausea.

IMPORTANT SAFETY INFORMATION

Allergy to Eggs or Egg Products
Tell your doctor if you have had a severe allergic reaction to eggs or egg products, as people with a known history of egg allergies were excluded from clinical trials.

Please see the Important Safety Information throughout and on page 11 and the accompanying full Prescribing Information for KANUMA® (sebelipase alfa).
PREPARING FOR YOUR KANUMA® (sebelipase alfa) INFUSIONS

BEFORE YOU GO

Bring these items to your first appointment:

• Your insurance card and ID (you may also want to call ahead to see if there are any other documents you will need)
• Items that may make you feel more comfortable (for example, a favorite pillow or blanket) during your infusion

WHEN YOU GET THERE

At the start of your appointment, you will:

• Check in with a receptionist who will look at your insurance card and ID, and may ask you to fill out some paperwork
• Meet with a healthcare provider, who may ask a few questions and check your blood pressure, temperature, breathing, pulse, and weight, as well as make other assessments
• Get set up in the space where you will be getting your infusion

IMPORTANT SAFETY INFORMATION

Common Side Effects
The most common side effects in patients treated with KANUMA® (sebelipase alfa) are:

• Infants with rapidly progressive LAL Deficiency presenting within the first 6 months of life (≥30%): diarrhea, vomiting, fever, stuffy or runny nose, anemia, cough, swelling of the nose and throat, and hives.
• Pediatric and adult patients with LAL Deficiency (≥8%): headache, fever, sore throat, swelling of the nose and throat, weakness, constipation, and nausea.

Please see the Important Safety Information throughout and on page 11 and the accompanying full Prescribing Information for KANUMA® (sebelipase alfa).

DURING YOUR INFUSION

• First, a healthcare provider will set up the IV equipment; if you are uncomfortable with needles, talk with your healthcare provider or doctor about strategies to make you feel more comfortable
• Once the infusion starts, your KANUMA® (sebelipase alfa) treatment will continue for at least 2 hours (though your doctor may decide to increase or decrease your infusion time)
• Tell your healthcare provider right away if you feel anything out of the ordinary or if you notice any of the following reactions during or after your infusion: rash such as hives (may also include itching), difficulty breathing, shortness of breath, tightness in the chest, and wheezing (noises while breathing), dizziness or feeling faint, tingling and swelling around the mouth, in your throat, or eyes, fast heartbeat, very low blood pressure, sweating, loss of consciousness, flushing or temporary reddening of the skin (usually on the face), or agitation or irritability.

AFTER YOUR INFUSION

• The IV or other device will be removed when the infusion is complete
• After your infusion, you may be asked to stay awhile so your healthcare provider can check your blood pressure, temperature, and pulse; if you do not feel well, let your healthcare provider know right away
• Tell your doctor or get medical help right away if you experience any of the following severe signs or symptoms at any time during or after your infusion: rash such as hives (may also include itching), difficulty breathing, shortness of breath, tightness in the chest, and wheezing (noises while breathing), dizziness or feeling faint, tingling and swelling around the mouth, in your throat, or eyes, fast heartbeat, very low blood pressure, sweating, loss of consciousness, flushing or temporary reddening of the skin (usually on the face), or agitation or irritability.
ONESOURCE™ SUPPORT SERVICES

With our experience and resources, we’re here to help you feel supported every step of the way. Here’s an overview of the services we offer.

Education
When you have questions about LAL-D or KANUMA® (sebelipase alfa), we’ll work to find the answers. Your dedicated Case Manager can provide you with:
- Educational materials about LAL-D
- Details about KANUMA
- Information about LAL-D

Health Insurance Navigation
Health insurance can be complicated. We’re here to help make sense of it all. Your Case Manager can help by:
- Providing information that explains your insurance coverage for KANUMA
- Addressing financial concerns or gaps in coverage

IMPORTANT SAFETY INFORMATION
Tell your doctor if you are pregnant or plan to become pregnant, or are breastfeeding or plan to breastfeed.

These are not all of the possible side effects of KANUMA. Call your healthcare provider for medical advice about side effects. To report suspected side effects contact Alexion at 1-844-259-6783 or the FDA at 1-800-FDA-1088.

Please see the Important Safety Information throughout and on page 11 and the accompanying full Prescribing Information for KANUMA® (sebelipase alfa).

Community Connections
With OneSource™ by your side, you’ll never have to go it alone.
Connect with others in the rare disease community who understand your experience. We can share information about:
- In-person and online meetings and events specific to your condition
- Support and resources
- Advocacy groups
- A peer-to-peer program called Peer Connects

Ongoing Support
When life takes a turn, OneSource is ready to keep you on track.
Your Case Manager is ready to help:
- Work with your healthcare provider to ensure you keep receiving your medicine as prescribed
- Guide you through insurance changes
- Navigate your treatment through life events, such as getting married, starting a new job, moving, or traveling

Get connected with your OneSource Case Manager by calling 1-888-765-4747, Monday through Friday, 8:30 AM to 8 PM (ET) or visit the website at www.alexiononesource.com.
KANUMA® (sebelipase alfa) INDICATION & IMPORTANT SAFETY INFORMATION

INDICATION:
KANUMA® is indicated for the treatment of people with a diagnosis of lysosomal acid lipase deficiency (LAL-D).

IMPORTANT SAFETY INFORMATION

Allergic Reaction
Life-threatening and severe allergic reactions may occur in people who receive KANUMA. These reactions may occur in people who are starting treatment with KANUMA or in people who have previously received KANUMA without having an allergic reaction. You should seek immediate medical care if any of these signs or symptoms that may be related to a severe allergic reaction occur:

- Rash such as hives; may also include itching
- Difficulty breathing, shortness of breath, tightness in the chest, and wheezing (noises while breathing)
- Dizziness or feeling faint
- Tingling and swelling around the mouth, in your throat, or eyes
- Fast heartbeat
- Very low blood pressure
- Sweating
- Loss of consciousness
- Flushing or temporary reddening of the skin (usually on the face)
- Agitation or irritability

Allergy to Eggs or Egg Products
Tell your doctor if you have had a severe allergic reaction to eggs or egg products, as people with a known history of egg allergies were excluded from clinical trials.

Common Side Effects
The most common side effects in patients treated with KANUMA are:

- Infants with rapidly progressive LAL Deficiency presenting within the first 6 months of life (≥30%): diarrhea, vomiting, fever, stuffy or runny nose, anemia, cough, swelling of the nose and throat, and hives.
- Pediatric and adult patients with LAL Deficiency (≥8%): headache, fever, sore throat, swelling of the nose and throat, weakness, constipation, and nausea.

Tell your doctor if you are pregnant or plan to become pregnant, or are breastfeeding or plan to breastfeed.

These are not all of the possible side effects of KANUMA. Call your healthcare provider for medical advice about side effects. To report suspected side effects contact Alexion at 1-844-259-6783 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the accompanying full Prescribing Information for KANUMA® (sebelipase alfa).
YOUR INFUSIONS WITH KANUMA® (sebelipase alfa)

- **KANUMA is an FDA-approved treatment for LAL-D.** KANUMA is administered by intravenous (IV) infusion and is available through a prescription.

- The most common side effects in people treated with KANUMA are:
  - Infants with rapidly progressive LAL-D presenting within the first 6 months of life (≥30%): diarrhea, vomiting, fever, stuffy or runny nose, anemia, cough, swelling of the nose and throat, and hives.
  - Pediatric and adult patients with LAL-D (≥8%): headache, fever, sore throat, swelling of the nose and throat, weakness, constipation, and nausea.

- **Your healthcare team will help you schedule your infusions with KANUMA.** Your infusions may take place in your doctor’s office, a hospital, or a specialized infusion center.

- **When you arrive, a healthcare provider will get you settled and set up your IV.** Once your IV is set up, the infusion begins and will last at least 2 hours, though your doctor may decide to increase or decrease your infusion time.

- **After your infusion, the IV will be removed and your healthcare provider will check in with you.** Your healthcare provider may check your blood pressure, temperature, and pulse.

- **Talk to your doctor about the importance of receiving regular infusions with KANUMA.**

Get connected with your OneSource™ Case Manager by calling 1-888-765-4747, Monday through Friday, 8:30 AM to 8 PM (ET) or visit the website at www.alexiononesource.com.

Please see the Important Safety Information on page 11 and the accompanying full Prescribing Information for KANUMA® (sebelipase alfa).

To learn more, visit [kanuma.com](http://kanuma.com)
INDICATIONS AND USAGE

KANUMA® is a hydrolytic lysosomal cholesterol ester and triacylglycerol-specific enzyme indicated for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency. (1)

DOSEAGE AND ADMINISTRATION

Infants with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life:

- The recommended starting dosage is 1 mg/kg as an intravenous infusion once weekly. (2.1)
- For patients with a suboptimal clinical response, increase the dosage to 3 mg/kg once weekly. (2.1)
- For patients with continued suboptimal clinical response, further increase the dosage to 5 mg/kg once weekly. (2.1)

Pediatric and Adult Patients with LAL Deficiency:

- The recommended dosage is 1 mg/kg as an intravenous infusion once every other week. (2.1)
- For patients with a suboptimal clinical response, increase the dosage to 3 mg/kg once every other week. (2.1)

See Full Prescribing Information for complete Dosage and Administration Information.

ADMINISTRATION INSTRUCTIONS

- Infuse over at least 2 hours. (2.3)
- Consider further prolonging the infusion time for patients receiving dosages greater than 1 mg/kg or for those who have experienced a hypersensitivity reaction. (2.3)
- Consider a 1-hour infusion for the 1 mg/kg dose in patients who tolerate the infusion. (2.3)
- A 1-hour infusion may be considered for those patients receiving dosages greater than 1 mg/kg or those who have experienced hypersensitivity reactions.
- A suboptimal clinical response is defined as any of the following: poor growth, development, organomegaly, or symptoms consistent with an anemia. (2.3)
- The recommended starting dosage is 1 mg/kg administered as an intravenous infusion once weekly. (2.3)
- For patients with a suboptimal clinical response, increase the dosage to 3 mg/kg once weekly. (2.3)
- For patients with continued suboptimal clinical response on the 3 mg/kg once weekly dosage, further increase the dosage to 5 mg/kg once weekly. (2.3)
- A suboptimal clinical response is defined as any of the following: poor growth, deteriorating biochemical markers, or persistent or worsening organomegaly.

Preparation Instructions

- Consider the risks and benefits of treatment in patients with known systemic hypersensitivity reactions to eggs or egg products. (2.3)
- For patients with continued suboptimal clinical response, increase the dosage to 5 mg/kg once weekly. (2.3)
- Pedantic and Adult Patients with LAL Deficiency:
- The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should be a clear, colorless to slightly colored solution. Thin, translucent particles or fibers may be present in the vials or diluted solution. Avoid the use of solutions that are cloudy or if other particulate matter is observed.
- The most common adverse reactions are:
- Hypersensitivity reactions including Anaphylaxis: Infants with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life: (≥30%): diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis, and urticaria. (6.1)
- Pediatric and Adult Patients with LAL Deficiency: (≥8%): headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation, and nausea. (6.1)
- Table 1: Total Infusion Volumes*

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>1 mg/kg dose</th>
<th>3 mg/kg dose</th>
<th>5 mg/kg dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 to 4.9</td>
<td>10</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>5 to 9.9</td>
<td>15</td>
<td>45</td>
<td>75</td>
</tr>
<tr>
<td>10 to 14.9</td>
<td>20</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>15 to 24.9</td>
<td>25</td>
<td>75</td>
<td>125</td>
</tr>
<tr>
<td>25 to 49.9</td>
<td>50</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>50 to 99.9</td>
<td>100</td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>100 to 120.9</td>
<td>200</td>
<td>500</td>
<td>1000</td>
</tr>
</tbody>
</table>

*The infusion volume should be based on the prescribed dose and should be prepared to a final KANUMA concentration of 0.1 mg/mL to 1.5 mg/mL.

2.3 Administration Instructions

Administer the diluted solution as an intravenous infusion using a low-protein binding infusion set with an in-line, low-protein binding 0.2 micron filter. Infuse over at least 2 hours. Consider further prolonging the infusion time for patients receiving dosages greater than 1 mg/kg or those who have experienced hypersensitivity reactions. Consider a 1-hour infusion for the 1 mg/kg dose in patients who tolerate the infusion. (2.3)

Adverse Reactions

- The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should be a clear, colorless to slightly colored solution. Thin, translucent particles or fibers may be present in the vials or diluted solution. Avoid the use of solutions that are cloudy or if other particulate matter is observed.

5. Warnings and Precautions

5.1 Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in KANUMA-treated patients, based on application of Sampson criteria to identify signs/symptoms consistent with anaphylaxis. In clinical trials, 3 (infants) of 106 (3%) patients treated with KANUMA experienced signs and symptoms consistent with anaphylaxis. These patients experienced reactions during infusion with signs and symptoms including chest discomfort, conjunctival injection, dyspnea, generalized and itchy rash, hyperemia, swelling of eyelids, rhinorrea, severe respiratory distress, tachycardia, tachypnea, and urticaria. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after treatment initiation. In clinical trials, 21 of 106 (20%) KANUMA-treated patients, including 9 of 14 (64%) infants and 12 of 92 (13%) pediatric patients who were 4 years and older, experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction. Signs and symptoms included:

- Hypersensitivity reactions including anaphylaxis: (≥30%): diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis, and urticaria. (6.1)
- Pediatric and Adult Patients with LAL Deficiency:
- The solution should be a clear, colorless to slightly colored solution. Thin, translucent particles or fibers may be present in the vials or diluted solution. Avoid the use of solutions that are cloudy or if other particulate matter is observed.

5.2 Hypersensitivity to Eggs or Egg Products

Notice to Healthcare Providers

KANUMA contains no preservatives; therefore, product should be used immediately after dilution. If immediate use is not possible, the diluted product may be stored up to 24 hours in the refrigerator or at 2°C to 8°C (36°F to 46°F) in a dry, cool and dark place, provided that the vials or diluted solution are covered. Avoid freezing. Do not use the solution if cloudy or if other particulate matter is observed.

Administration Directions

Administer the diluted solution as an intravenous infusion using a low-protein binding infusion set with an in-line, low-protein binding 0.2 micron filter. Infuse over at least 2 hours. Consider further prolonging the infusion time for patients receiving dosages greater than 1 mg/kg or those who have experienced hypersensitivity reactions. Consider a 1-hour infusion for the 1 mg/kg dose in patients who tolerate the infusion. (2.3)

5.3 Mix gently by inversion. Do not shake the vials or the prepared infusion.

5.4 The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should be a clear, colorless to slightly colored solution. Thin, translucent particles or fibers may be present in the vials or diluted solution. Avoid the use of solutions that are cloudy or if other particulate matter is observed.

5.5 Vials are for single-use only. Discard any unused product. Do not freeze.

6. Use in Specific Populations

6.1 Pregnancy

6.2 Lactation

6.3 Pediatric Use

6.4 Geriatric Use

11 Description

12 Clinical Pharmacology

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 Clinical Studies

14.1 Infants with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life

14.2 Pediatric and Adult Patients with LAL Deficiency

15 How Supplied/Storage and Handling

16 Patient Counseling Information

*Sections or subsections omitted from the full prescribing information are not listed.
symptoms of hypersensitivity reactions, occurring in two or more patients, included abdominal pain, agitation, fever, chill, diarrhea, eczema, edema, hypertension, irritability, laryngeal edema, nausea, pallor, pruritus, rash, and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion. Patients were not routinely pre-medicated prior to infusion of KANUMA in these clinical trials.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when KANUMA is administered. If anaphylaxis occurs, immediately discontinue the infusion and initiate appropriate medical treatment. Observe patients closely during and after the infusion. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should signs and symptoms occur.

The management of hypersensitivity reactions should be based on the severity of the reaction and may include temporarily interrupting the infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids. If interrupted, the infusion may be resumed at a slower rate with increases as tolerated. Pre-treatment with antipyretics and/or antihistamines may prevent subsequent reactions in those cases where symptomatic treatment was required. If a severe hypersensitivity reaction occurs, immediately discontinue the infusion and initiate appropriate medical treatment.

Consider the risks and benefits of re-administering KANUMA following a severe reaction. Monitor patients, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

5.2 Hypersensitivity to Eggs or Egg Products

KANUMA is produced in the egg whites of genetically engineered chickens. Patients with a known history of egg allergies were excluded from the clinical trials. Consider the risks and benefits of treatment with KANUMA in patients with known systemic hypersensitivity reactions to eggs or egg products.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In clinical trials, a total of 106 patients received treatment with KANUMA. The data described below reflect exposure to KANUMA in 75 patients who received KANUMA at dosages up to 3 mg/kg once weekly during the double-blind period of study treatment.

- Nine patients (5 males, 4 females) who had growth failure or other evidence of rapidly progressive LAL deficiency presenting within the first 6 months of life received KANUMA for up to 165 weeks (median 60 weeks) at escalating doses ranging between 0.35 mg/kg and 5 mg/kg once weekly. (see Clinical Studies (14.1))
- 66 pediatric and adult patients with LAL deficiency aged 4 to 58 years (33 males, 33 females) received KANUMA 1 mg/kg every other week for up to 36 weeks.

Table 2 summarizes the most common adverse reactions occurring in >30% of patients with rapidly progressive LAL deficiency presenting within the first 6 months of life receiving KANUMA in Study 1.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>KANUMA (N=9)</th>
<th>Placebo (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (67)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>5 (56)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (56)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3 (33)</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (33)</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>3 (33)</td>
<td></td>
</tr>
</tbody>
</table>

Other less common adverse reactions reported in patients with rapidly progressive disease presenting within the first 6 months of life who received KANUMA included anxiety and chest discomfort.

Table 2: Adverse Reactions in ≥30% of Patients with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life Receiving KANUMA

For pediatric and adult patients (n = 106), the following additional adverse reactions were reported in ≥8% of pediatric and adult patients who received Kanuma since the time of marketing authorization, including patients who received an escalated dose to 3 mg/kg qw: hypersensitivity, diarrhea, abdominal pain, and dizziness.

Increases in circulating LDL-cholesterol (LDL-c) and triglycerides above pre-treatment values were observed in 29 of 36 (81%) and 21 of 36 (58%) patients, respectively, at 2 and 4 weeks following initiation of KANUMA (see Clinical Pharmacology (12.2)). The maximum mean percentage increase was 18% for LDL-c at Week 2 and 5% for triglycerides at Week 4.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the clinical trials to the incidence of antibodies in other studies or to other sebelipase alfa products may be misleading.

Approximately 8% (9/106) of pediatric and adult patients with LAL deficiency developed antibodies to sebelipase alfa (anti-drug antibodies or ADA) following treatment with KANUMA across all clinical studies. Among the 9 patients who developed ADA, 2 patients were positive for neutralizing antibodies (NAb). Approximately 53% (10/19) of infants with rapidly progressive LAL deficiency developed ADA following treatment with KANUMA across all clinical studies. Among the 10 patients who developed ADA, 9 patients were positive for NAb.

5.3 ADA Titers

The amino acid sequence for sebelipase alfa is the same as the amino acid sequence for human glycoprotein enzyme produced by recombinant DNA technology in the egg white of eggs containing 6 N-linked glycosylation sites and has a molecular mass of approximately 55 kDa.

Five of 35 (14%) KANUMA-treated pediatric and adult patients who completed the 20-week double-blind period of study treatment developed ADA. All patients were receiving 1 mg/kg once every other week. All 5 ADA-positive patients first developed measurable ADA titers within the first 3 months of exposure. Two of the 5 ADA-positive patients had a measurable ADA titer at only one time point. In 3 of the 4 ADA titer at multiple time points, ADA titers decreased to undetectable levels during continued treatment. Two patients developed in vitro neutralizing antibodies during the open-label extension phase after 20 weeks and 52 weeks of treatment with KANUMA, respectively. There is no clear association between the development of ADA and decreased efficacy in pediatric and adult patients treated with KANUMA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with KANUMA use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Animal reproductive studies conducted with sebelipase alfa showed no evidence of embryofoetal lethality, fetotoxicity, teratogenicity, or abnormal early embryonic development at dosages up to 164 and 526 times the human dosage of 1 mg/kg every other week (based on AUC) in rats and rabbits, respectively.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Animal Data

Sebelipase alfa administered during the period of organogenesis to rats on gestation days 6, 9, 12, 15 and 17 and rabbits (on gestation days 7, 10, 13, 16 and 19) at intravenous doses ranging between 0.35 mg/kg and 5 mg/kg respectively, (approximately 164 and 526 times the human AUC of 1387 ng/mL at 1 mg/kg dose administered once every other week, respectively) did not cause any adverse effects on embryofoetal development. A pre- and post-natal development study in rats showed no evidence of embryolethality, reproductive studies conducted with sebelipase alfa showed no evidence of embryofoetal lethality, ketotocicity, teratogenicity, or abnormal early embryonic development at dosages administered on gestation days 6, 9, 12, 15, 18, and 20 and days 4, 7, 10, 14, and 17 (postpartum) of sebelipase alfa up to 60 mg/kg/day (approximately 164 times the human AUC of 1387 ng/mL at 1 mg/kg dose administered once every other week).

8.2 Lactation

Risk Summary

There are no data on the presence of sebelipase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known if sebelipase alfa is present in animal milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for KANUMA and any potential adverse effects on the breastfed infant from sebelipase alfa or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of KANUMA have been established in pediatric patients aged 1 month and older. Clinical trials with KANUMA were conducted in 56 pediatric patients (range 1 month to <18 years old) (see Clinical Studies (14)).

8.5 Geriatric Use

Clinical trials of KANUMA did not include any patients aged 65 years old and older. It is not known whether they respond differently than younger patients.

11 DESCRIPTION

Sebelipase alfa is a recombinant human lysosomal acid lipase (hLAL) that is a lysosomal glycoprotein enzyme produced by recombinant DNA technology in the egg white of eggs laid by genetically engineered chickens. Purified sebelipase alfa is a monomeric glycoprotein containing 6 N-linked glycosylation sites and has a molecular mass of approximately 55 kDa.

The amino acid sequence for sebelipase alfa is the same as the amino acid sequence for human LAL. The specific activity of sebelipase alfa is 195 to 345 units/mg. One unit is the amount of enzyme activity that catalyzes the hydrolysis of 1 micromole of the synthetic substrate 4-methylumbelliferyl oleate per minute at 37°C under specified assay conditions.
KANUMA (sebelipase alfa) injection is supplied as a sterile, preservative-free, non-pyrogenic clear to slightly opalescent, colorless to slightly colored aqueous solution in single-dose vials for intravenous infusion. Each vial contains sebelipase alfa 20 mg/10 mL. Each mL of solution contains sebelipase alfa (2 mg), citric acid monohydrate (1.57 mg), Human Serum Albumin (10 mg), and triisodium citrate dihydrate (13.7 mg) at pH 5.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
LAL deficiency is an autosomal recessive lysosomal storage disorder characterized by a genetic defect resulting in a marked decrease or loss in activity of the lysosomal acid lipase (LAL) enzyme. The primary site of action of the LAL enzyme is the lysosome, where the enzyme normally causes the breakdown of lipid particles, including LDL-c and triglycerides. Deficient LAL enzyme activity results in progressive complications due to the lysosomal accumulation of cholesteryl esters and triglycerides in multiple organs, including the liver, spleen, intestine, and the walls of blood vessels. The resulting liver accumulation in the liver may lead to increased liver fat content and progression of liver disease, including fibrosis and cirrhosis. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. In parallel, dyslipidemia due to impaired degradation of lysosomal lipid is common with elevated LDL-c and triglycerides and low HDL-cholesterol (HDL-c).

Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.

12.2 Pharmacodynamics
In clinical trials, after initiation of dosing with KANUMA, breakdown of accumulated lysosomal lipid and subsequent reductions in serum lipids were observed in all patients who received KANUMA dose escalation. The pharmacokinetic profile of sebelipase alfa was nonlinear with a greater than dose-proportional increase in clearance and decreases in HDL-c.

In all patients with elevated alanine aminotransferase (ALT) values at baseline (82 of 84 patients in clinical trials), reductions in ALT values were observed, generally within 2 weeks after initiation of treatment with KANUMA. The pharmacokinetic profile of sebelipase alfa was similar between adolescents and adults. The Tmax and T1/2 were similar across all age groups.

### Table 4: Mean (SD) Pharmacokinetic Parameters at Week 22 in Pediatric and Adult Patients Receiving 1 mg/kg Once Every Other Week

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4-11 years old</th>
<th>12-17 years old</th>
<th>≥18 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng.h/mL)</td>
<td>942 (388)</td>
<td>1454 (699)</td>
<td>1861 (599)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>490 (205)</td>
<td>784 (480)</td>
<td>957 (303)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.3 (0.6)</td>
<td>1.1 (0.3)</td>
<td>1.3 (0.6)</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>31.1 (7.1)</td>
<td>37.4 (12.4)</td>
<td>38.2 (12.5)</td>
</tr>
<tr>
<td>V (L)</td>
<td>3.6 (3.0)</td>
<td>5.4 (2.4)</td>
<td>5.3 (1.6)</td>
</tr>
<tr>
<td>T1/2 (min)</td>
<td>5.4 (3.3)</td>
<td>6.6 (3.7)</td>
<td>6.6 (3.7)</td>
</tr>
</tbody>
</table>

Parameter values were estimated using a population pharmacokinetic model.

AUC = Area under the plasma concentration time curve. Cmax = Maximum concentration. Tmax = Time to maximum concentration. CL = Clearance. V = Central volume of distribution. T1/2 = Half-life.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with sebelipase alfa. Sebelipase alfa at intravenous doses up to 60 mg/kg administered twice weekly (approximately 164 times the human AUC of 1387 ng.h/mL at 1 mg/kg dose administered once every other week) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology
In a rat dose model of LAL deficiency that exhibits several abnormalities analogous to the human disease, sebelipase alfa administered intravenously at dosages up to 3 mg/kg once weekly showed improvements in survival, body weight gain, organ weight reduction, reduction in serum transaminases (ALT and aspartate aminotransferase [AST]), reduction in serum and hepatic lipids, and improvement in liver histopathology.

14 CLINICAL STUDIES

14.1 Infants with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life
A multicenter, open-label, single-arm clinical study of KANUMA was conducted in 9 infants with LAL deficiency who had growth failure or other evidence of rapidly progressive disease prior to 6 months of age. The age range at entry was 1 to 6 months. Patients received KANUMA at 0.35 mg/kg once weekly for the first 2 weeks and then 1 mg/kg once weekly. Due to suboptimal clinical response, doses in all 6 surviving patients were escalated to 3 mg/kg once weekly, between 41 and 188 weeks (median 11 weeks) after starting treatment at 1 mg/kg.

The efficacy of KANUMA was assessed by comparing the survival of the 9 KANUMA-treated patients (followed in the open-label, single-arm trial) at 12 months of age to the survival in an untreated, historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Of the 9 KANUMA-treated patients, 6 patients survived beyond 12 months of age, compared to 0 of 21 patients who survived in the historical cohort, all of whom had died by 8 months of age. The median age of the 6 surviving KANUMA-treated patients was 18.1 months (range 12 to 42.2 months).

Continuation Treatment
Across Study 1 and another study, Study 3, in infants with rapidly progressive LAL Deficiency, 9 patients received successive dose escalations up to 5 mg/kg once weekly due to suboptimal clinical response.[See Recommended Dose (2.1)]. The median duration of exposure to 5 mg/kg for 9 of 11 patients whose doses were escalated to 5 mg/kg overall was 33 months (range 27 to 39 months) for patients in Study 1 and 15 months (range 5 to 24 months) for patients in Study 3. Of the 9 patients whose KANUMA dose was escalated to 5 mg/kg once weekly, 6 were alive at their last follow up at 3 years, and 2 were alive at their last follow up at 5 years. Of these 9 patients, 6 experienced normalized ALT and/or AST which had remained abnormal on the lower KANUMA dose.

14.2 Pediatric and Adult Patients with LAL Deficiency
The safety and efficacy of KANUMA were assessed in 66 pediatric and adult patients with LAL deficiency, aged 4 to 58 years (71% were less than 18 years old), in a multicenter, double-blind, placebo-controlled trial. Patients were randomized to receive KANUMA at a dosage of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. Sixty-two of the 66 (94%) patients had LDL-c of 130 mg/dL or greater at study entry. The majority of patients (58%) had LDL-c above 190 mg/dL at study entry, and 24% of patients with LDL-c above 190 mg/dL remained on lipid lowering medications.

In the 20-week double-blind period of the trial, a statistically significant improvement in percent change from baseline in LDL-c was observed in the KANUMA-treated group as compared to the placebo group (mean difference and 95% CI: -22%, [-33%, -13%]; p<0.0001). LDL-c of less than 130 mg/dL was achieved in 13 of 32 (41%; 95% CI: [24%, 58%]) KANUMA-treated patients and only in 2 of 30 (7%; 95% CI: [0%, 16%]) placebo-treated patients with baseline LDL-c of 130 mg/dL or greater. A statistically significant improvement in percent change from baseline to 20 weeks was also observed in the KANUMA-treated group compared to placebo in patients for other parameters related to LAL deficiency, including decreases in non-HDL-c (mean difference and 95% CI: -21%, [-30%, -15%]; p<0.0001) and triglycerides (mean difference and 95% CI: -14%, [-28%, -1%]; p=0.0375), and increases in HDL-c (mean difference and 95% CI: 20%, [12%, 26%]; p<0.0001). The effect of KANUMA on cardiovascular morbidity and mortality has not been established.

Patients treated with KANUMA had larger reductions from baseline in ALT values and liver fat content (measured by MRI), compared to patients treated with placebo. The significance of these findings as they relate to progression of liver disease in LAL deficiency has not been established.

15 HOW SUPPLIED/STORAGE AND HANDLING
KANUMA (sebelipase alfa) injection is a preservative-free, clear to slightly opalescent, colorless to slightly colored, nonpyrogenic solution supplied as 20 mg/10 mL (2 mg/mL) in single-dose, glass vials.

NDC 25682-007-01: 20 mg/10 mL vial
Store KANUMA refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not shake or freeze the vials.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions, Including Anaphylaxis
Advise patients and caregivers that reactions related to administration and infusion may occur during and after KANUMA treatment, including anaphylactic reactions, life-threatening anaphylaxis and severe hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylactic reactions, anaphylaxis and hypersensitivity reactions, and have them seek immediate medical care should signs and symptoms occur.[See Warnings and Precautions (5.1)].

Patients are warned not to touch, ingest, or inhale KANUMA. KANUMA is produced in the egg whites of genetically engineered chickens. Patients with a known history of egg allergies were excluded from the clinical trials. Consider the risks and benefits of treatment with KANUMA in patients with known systemic hypersensitivity reactions to eggs or egg products.[See Warnings and Precautions (5.2)].

Manufactured by:
Aexion Pharmaceuticals, Inc.
121 Seaport Boulevard,
Boston MA 02210 USA
US License Number: 713
1-888-765-4747 (phone)

© 2022 Aexion Pharmaceuticals, Inc.