Strensiq®
(asfotase alfa) for injection | 40 mg/mL

FACE YOUR FEARS WITH STRENSIQ

Replace what's missing.
Replace fear with courage.

INDICATION

What is STRENSIQ® (asfotase alfa)?
STRENSIQ is a prescription medicine used to treat people with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

SELECT IMPORTANT SAFETY INFROMATION

The most common side effects of STRENSIQ include local skin injection-site reactions (red skin patches, bruising, color change, pain, itching, thinning, swelling, pits, and bumps) and calcium buildup in your eyes and kidneys.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

Click here for Caregiver side

IT TAKES COURAGE TO LIVE WITH HYPOPHOSPHATASIA

When you are living with hypophosphatasia (HPP), the world can be scary. Everyday actions, such as walking across the street or playing with friends, may result in injuries – a lost tooth or joint pain. This rare condition can leave you feeling alone and in the dark.

Although receiving a diagnosis of HPP is not easy, you can move forward with courage because there is an FDA-approved treatment available and a personalized patient support program from Alexion. There is hope for the future. And there is a rare disease community that cares.

Unmasking HPP

Most of us take our bones for granted. And yet, our overall well-being depends upon the health of our skeletal structure. Not only do our bones support and protect the human body and help us move through the world, they also produce blood cells and store essential minerals that our bodies need to remain healthy.

When your body lacks sufficient alkaline phosphatase (ALP) enzyme, you develop weak or "soft" bones, which may lead to skeletal deformities, tooth loss or pain, or other related symptoms. Simple tasks, such as climbing stairs, rising from a seated position, or walking, can become difficult, limiting daily activity. And even though HPP is a disease of bone mineralization, it may have an effect on many other aspects of your health. In short, life with HPP can be scary...but there's help.

> "They say what you don't know won't hurt you, but that's not how it worked for me. It was only after I was diagnosed with HPP, that I began to really be able to live my life."
>
> – Jonathan, living with HPP

Discover Confidence with STRENSIQ® (asfotase alfa)

STRENSIQ is the only ALP enzyme replacement therapy for people with perinatal/infantile-onset and juvenile-onset HPP. Taken at home, STRENSIQ is an injectable prescription medication that provides skeletal healing and improved mobility.

JONATHAN
Living with HPP

To learn more about STRENSIQ, visit STRENSIQ.com.

Select Important Safety Information

STRENSIQ may cause serious side effects, including serious allergic (hypersensitivity) reactions happened in some people who use STRENSIQ. Stop using STRENSIQ and go to the nearest hospital emergency room right away if you or your loved one have any of the signs and symptoms of a serious allergic reaction, including difficulty breathing, swelling of your eyes, lips, or tongue, hives, feeling faint, nausea or vomiting, dizziness, itching of your lips, tongue, or throat, and choking sensation.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

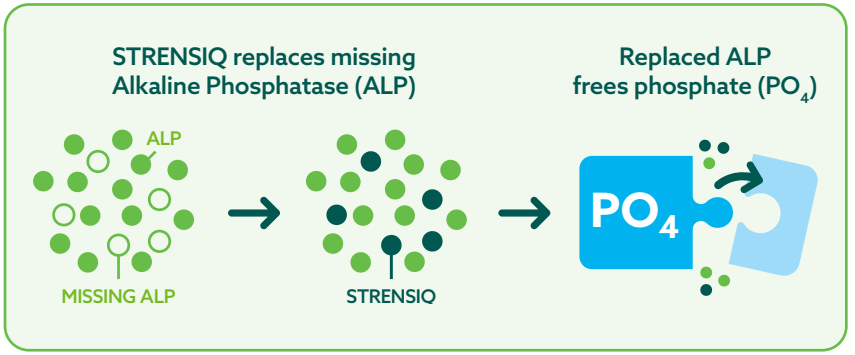
REPLACE FEAR WITH CONFIDENCE

Until recently, people diagnosed with HPP had no approved treatment for this rare disease. Today, there's STRENSIQ® (asfotase alfa), the only FDA-approved prescription medicine that replaces the alkaline phosphatase (ALP) enzyme in the body to treat people with perinatal/infantile-onset and juvenile-onset HPP. STRENSIQ provides skeletal healing and improved mobility.

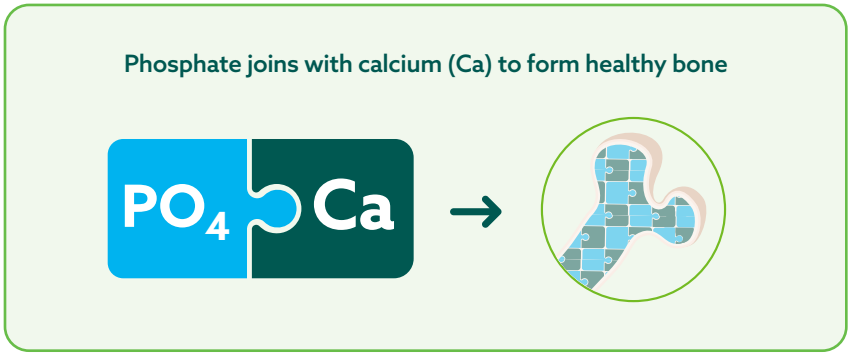
> "As a parent, there have been good days and bad days living with this disease. I learned to adapt and do things from a wheelchair. My youngest went to a father-daughter square dance with me in a manual wheelchair. It made me quite dizzy to spin in that wheelchair, but it was worth it to see the joy in my youngest daughter's heart."
>
> – David, living with HPP

To learn more about STRENSIQ, visit STRENSIQ.com.

Calcium and phosphate are two of the essential components needed to create and maintain healthy bones. But people born with HPP don't have enough active ALP enzyme, which is needed to "mineralize" bones. ALP frees phosphate so it can combine with calcium and form the building blocks needed to make bone.



STRENSIQ replaces the ALP your body needs to build healthy bones.



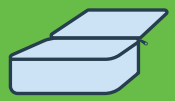
It is important to note that every patient is different. How you respond to treatment may vary from how other patients respond.

Select Important Safety Information
STRENSIQ may cause serious side effects, including skin thickening or pits at the injection site (lipodystrophy) has happened several months after using STRENSIQ.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

STARTING STRENSIQ® (asfotase alfa)

Beginning any journey takes courage – and Alexion is there to guide you every step of the way. Once your doctor prescribes STRENSIQ to treat your HPP, you'll be provided additional resources to begin your treatment with confidence.



Turn to page 22a to find out more about the tools available to help you live fearlessly with HPP. Have questions about starting or staying on STRENSIQ? Find the answers with OneSource™.

"OneSource was recommended to me by an advocacy organization when I initially thought I might have HPP. After reaching out to OneSource, I was paired with a OneSource Case Manager. She was there to help me even before diagnosis."

- Ray, living with HPP

STAYING ON STRENSIQ

STRENSIQ is given as an injection under the skin (called a subcutaneous injection) and can be conveniently taken at home or wherever you go. Your doctor will prescribe a specific dose of STRENSIQ based on your weight and will decide how often it should be given.

STRENSIQ is available as either one milligram per kilogram of body weight, six times per week, or two milligrams per kilogram of body weight, three times per week. You and your doctor will work together to determine the dosage that's right for you. As your weight changes, your dosage may also change depending on your doctor's recommendations.

It is important to use STRENSIQ as described in the Patient Prescribing Information and Instructions for Use, or as instructed by your doctor, nurse, or pharmacist.

Turn to page 21a to find out how to receive additional Alexion materials, including your STRENSIQ Starter Kit and Injection Starter Kit.

Find Your Injection Courage

Confidence grows when you have a consistent injection routine that works for you. Once you receive your first shipment of STRENSIQ, you will also receive the Injection Starter Kit. Inside, you'll find guidance on how to administer injections and tools for how to develop a routine that works for you.

Select Important Safety Information

STRENSIQ may cause serious side effects, including: Calcium buildup in the eyes and kidneys can occur if you or your loved one have HPP. Your healthcare provider should check the eyes and kidneys while you or your loved one use STRENSIQ. **Decreased efficacy.** Contact your healthcare provider if you or your loved one notice STRENSIQ is no longer working or experience worsening symptoms of HPP (e.g., increased respiratory support, increased difficulty walking, new fractures).

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

CONFIDENT CONVERSATIONS

Taking an active role in your HPP treatment journey can make a difference in your health. Even after diagnosis, it's important to communicate honestly with your treating physician about your life with HPP. To prepare for your next visit, use your STRENSIQ® (asfotase alfa) Treatment Journal and Symptom Tracker to write down questions and keep a record of symptoms for your doctor.

Conversation Starters

1. What improvements can be expected with STRENSIQ? How will you measure these improvements?
2. What are the possible side effects of STRENSIQ?
3. How long will I need to stay on STRENSIQ?
4. Will the dose of STRENSIQ change with my age, or if I lose or gain weight?
5. Does STRENSIQ affect any other medications I am taking?
6. Once STRENSIQ is started, how often should I visit the doctor?
7. How can STRENSIQ affect my lab test results? (See page 21a for a detailed description of Medical Alert Card)
8. How will HPP impact my family members?

> "When people ask about HPP, I'm frank, direct, and unapologetic. I tell them I take an injection to make my bones healthier. I equate it to any other type of medication that people take for chronic conditions. Comparing it to something people know makes it easier for them to understand. I'm very matter of fact. HPP is part of who I am."
>
> – Jonathan, living with HPP

To learn more about STRENSIQ, visit STRENSIQ.com.

SOURCES OF SUPPORT

Need a confidence boost? There is a community of support waiting to help you!

When you need information about HPP and its treatment, **OneSource™**, a complimentary patient support program from Alexion, is there to help. After signing up, you will be matched with a dedicated OneSource Case Manager who can answer any questions you may have about HPP or STRENSIQ® (asfotase alfa).

OneSource Case Managers are skilled professionals who provide one-to-one education and support for people living with HPP and their caregivers.

Your Case Manager is your primary contact for the OneSource program and is here to help you throughout your journey.

Turn to page 21a to find out how to receive additional Alexion materials, including your STRENSIQ Starter Kit and Injection Starter Kit.

PANTHERx Rare is a specialty pharmacy that serves the needs of HPP patients. PANTHERx will work with your doctor and insurance company to help get you access to STRENSIQ. In addition, PANTHERx provides ongoing support and communication around any insurance challenges and continued shipments of medication.

TRAVEL TIPS: ON THE GO WITH STRENSIQ

When traveling with STRENSIQ, keep it refrigerated throughout your trip. STRENSIQ should be refrigerated in its original package at 36°F to 46°F (2° to 8°C) and protected from light. Before you head out on your next trip, remember the following instructions:

1. **Plan Ahead:** Gather your injection supplies and check with your destination to make sure there will be a place to refrigerate STRENSIQ when you arrive.
2. **Keep Cool:** To maintain its ideal temperature, STRENSIQ may be stored in an insulated cooler. If traveling long distances by plane, call ahead to your airline to find out if refrigeration is provided in-flight. Always travel with STRENSIQ in your carry-on luggage. Do not store STRENSIQ in your checked luggage.

Planning a trip? Remember, your Injection Starter Kit includes a travel letter that can be shown to airline staff to make sure your STRENSIQ travels with you appropriately.

Select 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 the possible side effects of STRENSIQ. For more information, ask your healthcare provider or pharmacist. Call your healthcare provider for medical advice about side effects. You may report side effects to the US Food and Drug Administration at 1-800-FDA-1088.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

FIND CONFIDENCE IN COMMUNITY

HPP is a rare disease, but you're not alone. There's a community of people living with HPP ready to support and encourage you.

One of the best ways to find community and support is to hear stories of courage and hope from our **HPP STARS**, people living with HPP and their caregivers.

Join Us at a Live HPP Event or Webinar

Throughout the year, Alexion sponsors **Unmask HPP** webinars and live events for people living with HPP and their caregivers, featuring **HPP STARS** sharing their stories. For more information and to register, go to AlexionHPPEvents.com

HPP Support Groups

Soft Bones (softbones.org) provides information and a community to educate, empower, and connect people living with HPP and their families and caregivers.

MAGIC Foundation (magicfoundation.org) provides support services for the families of children with a wide variety of chronic and/or critical disorders, syndromes, and diseases that affect a child's growth.

The Avalon Foundation (kidscaringforkids.org) provides emotional and educational support to families receiving care for HPP.

The HPP support groups listed above are independent, nonprofit patient service organizations. Their listing in this brochure does not imply endorsement of any product or company. All logos and trademarks are the property of their respective owners.

INDICATION & IMPORTANT SAFETY INFORMATION for STRENSIQ® (asfotase alfa) 40mg/mL vial

INDICATION
What is STRENSIQ?
STRENSIQ is a prescription medicine used to treat people with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

IMPORTANT SAFETY INFORMATION
What are the possible side effects of STRENSIQ?
STRENSIQ may cause serious side effects, including

- **Serious allergic (hypersensitivity) reactions** happened in some people who use STRENSIQ. Stop using STRENSIQ and go to the nearest hospital emergency room right away if you or your loved one have any of the signs and symptoms of a serious allergic reaction, including
  - Difficulty breathing
  - Swelling of your eyes, lips, or tongue
  - Hives
  - Feeling faint
  - Nausea or vomiting
  - Dizziness
  - Itching of your lips, tongue, or throat
  - Choking sensation
- **Skin thickening or pits at the injection site (lipodystrophy)** has happened several months after using STRENSIQ.
- **Calcium buildup in the eyes and kidneys** can occur if you or your loved one have HPP. Your healthcare provider should check the eyes and kidneys while you or your loved one use STRENSIQ.
- **Decreased efficacy.** Contact your healthcare provider if you or your loved one notice STRENSIQ is no longer working or experience worsening symptoms of HPP (e.g., increased respiratory support, increased difficulty walking, new fractures).

The most common side effects of STRENSIQ include local skin injection-site reactions (red skin patches, bruising, color change, pain, itching, thinning, swelling, pits, and bumps) and calcium buildup in your eyes and kidneys.

STRENSIQ may affect other lab test results, therefore it is important that you present your Medical Alert Card to your healthcare team so they are aware that you are being treated with an alkaline phosphatase (ALP) replacement therapy which may cause incorrect results on certain laboratory tests.

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

These are not all the possible side effects of STRENSIQ. For more information, ask your healthcare provider or pharmacist. Call your healthcare provider for medical advice about side effects. You may report side effects to the US Food and Drug Administration at 1-800-FDA-1088.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

HOW STRENSIQ® (asfotase alfa) HELPS

Fear Less: STRENSIQ Improves Bone Health and Increases Mobility[1]

STRENSIQ was studied in children and adults, but only in those with signs and symptoms that appeared before 18 years of age.

	STUDY 1	STUDY 2	STUDY 3	STUDY 4
Initial Ages	Up to 3 years	Up to 5 years	6 to 12 years	13 to 65 years
When did HPP symptoms start?	Before 6 months of age	Before 6 months of age	Before 18 years of age	Before 18 years of age (for 18 of the 19 study patients)
Number of People in Study	11	69	13	19
Primary Endpoints	Improvements in HPP[2]-related bone health/ mineralization	Improvements in HPP-related bone health/ mineralization	Improvements in HPP-related bone health/ mineralization	Changes in PPi and PLP[3] blood levels
Select Additional Endpoints	Growth[4] and survival	Growth and survival	Growth and **mobility**	**Mobility** and bone health/ mineralization

Select Secondary Endpoints presented in this brochure are in bold in the table above

[1] **Mobility** is a person's ability to walk.

[2] **HPP** is when your body lacks sufficient ALP[5] enzyme, you develop weak or "soft" bones, which may lead to skeletal deformities, tooth loss or pain, or other related symptoms.

[3] **PPi and PLP** are substances found in blood that are related to ALP activity and bone health.

[4] **Growth** refers to changes in body size based on age over time.

[5] **ALP** is an enzyme, which is needed to "mineralize" bones. ALP frees phosphate so it can combine with calcium and form the building blocks needed to make bone.

STUDY 1 AND 2: STRENSIQ IMPROVES SKELETAL HEALING

Study 1 & 2 Primary Endpoints

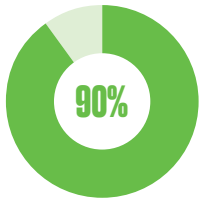
Improvements in HPP-related bone health/mineralization

Study 1 included patients up to 3 years of age with signs and symptoms that appeared before six months of age. At six months, 90% (n=10) of patients responded to treatment, which was sustained at seven years (n=7).

Study 2 included patients up to 5 years of age with signs and symptoms that appeared before six months of age. At six months, 63% (n=64) of patients responded to treatment, which was sustained at six years (n=2).

STUDY 1:

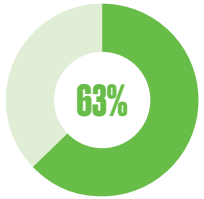
AFTER 6 MONTHS OF STRENSIQ
treatment achieved complete or substantial bone healing



AFTER 7 YEARS OF STRENSIQ
treatment achieved complete or substantial bone healing

STUDY 2:

AFTER 6 MONTHS OF STRENSIQ
treatment achieved complete or substantial bone healing



AFTER 6 YEARS OF STRENSIQ
treatment achieved complete or substantial bone healing

SKELETAL HEALING: STRENSIQ® (asfotase alfa) IMPROVES BONE HEALTH

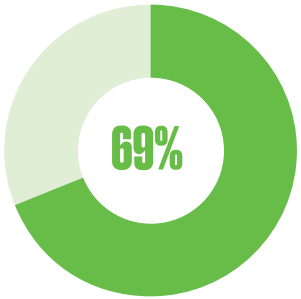
Study 3 Primary Endpoint

Improvements in HPP-related bone health/mineralization
Study 3 included patients from ages 6 years to 12 years with signs and symptoms that appeared before 18 years of age.

At six months, 69% (n=13) of patients responded to treatment, which was sustained at seven years (n=12).

- 1 child did not complete this study

AFTER 6 MONTHS OF STRENSIQ
treatment achieved complete or substantial bone healing

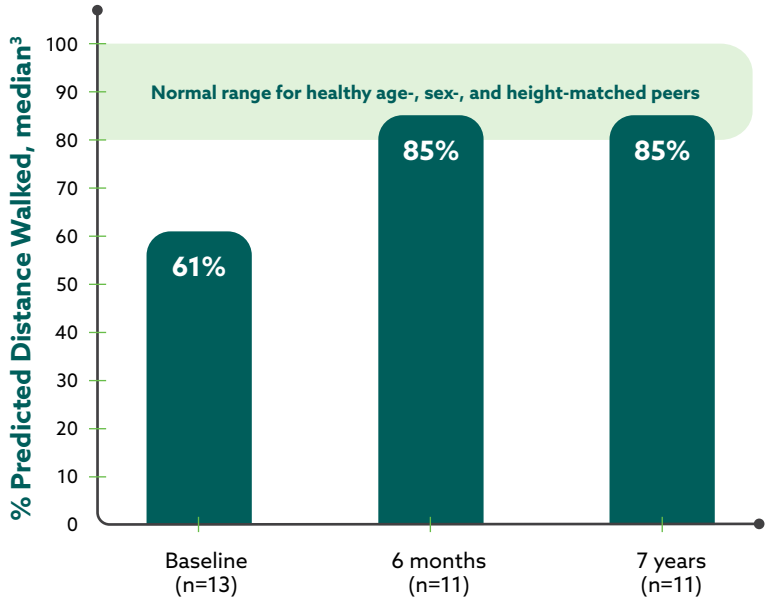


AFTER 7 YEARS OF STRENSIQ
treatment achieved complete or substantial bone healing

IMPROVEMENTS IN MOBILITY[1]: 6-MINUTE WALK TEST

Study 3 Select Secondary Endpoint

Mobility
Six-minute Walk Test (6MWT)[2] was conducted in 11 out of 13 children aged 6-12 with HPP during the study. In the 11 children, the % of their predicted[3] walking distance reached the normal range after 6 months of treatment and improvements were sustained over seven years.



[1] **Mobility** is a person's ability to walk.
[2] **6MWT** is the distance walked measured over a 6-minute time period.
[3] This refers to the percentage of the distance a healthy person of similar age, gender, and height would be expected to walk in 6 minutes.

CHANGE IN PLASMA PPi[1] AND PLP[2]

Study 4 Design

- Study 4 spanned five years and included adolescents and adults ages 13 to 65 years with signs and symptoms of HPP that appeared before 18 years of age (for 18 of the 19 study patients).
- The primary endpoints of this study were to measure reductions of PPi and PLP, which are substances found in the blood that are related to ALP enzyme activity and bone health. If PPi and PLP are high, ALP activity is generally low.
- The most frequently reported adverse events were injection-site reactions.
- This data is not included in the FDA-approved Prescribing Information.
- Over the initial duration of the study, STRENSIQ was administered at lower doses than the FDA-approved dose (weight-based dose of 6mg/kg per week).

Study 4 Primary Endpoints

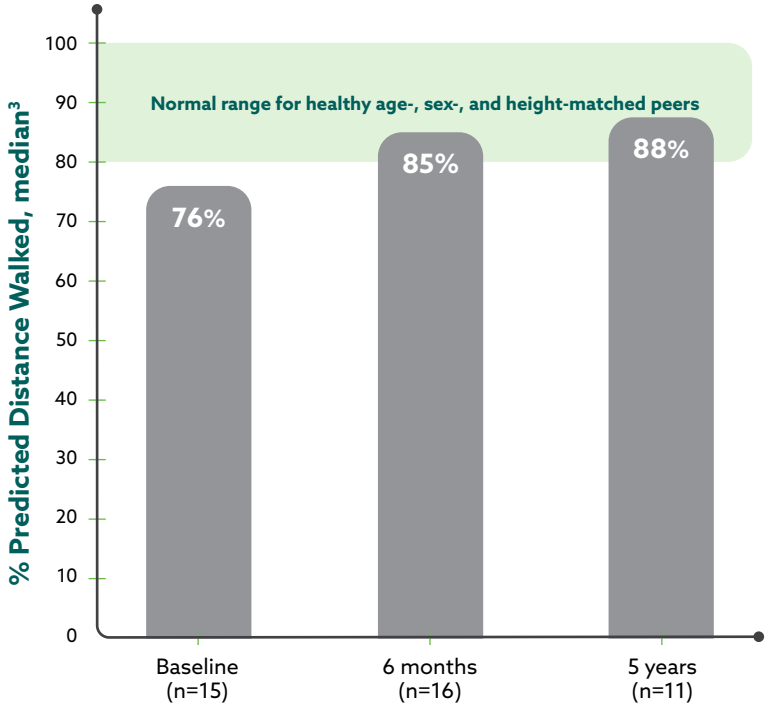
PLP and PPi
The study's two co-primary endpoints were to measure the change in blood levels of two known substances related to ALP activity at six months: PPi and PLP. While the co-primary endpoint was not significant, individually, the change in PLP levels at 6 months was significant.

☒ **PPi: was not significant** ☑ **PLP: significant**

IMPROVEMENTS IN MOBILITY WHILE BEING TREATED WITH STRENSIQ

Study 4 Select Secondary Endpoint

Mobility
Improvement in the 6-Minute Walk Test (6MWT) was observed as early as 6 months and sustained through 5 years.



[1] **PPi** stands for **inorganic pyrophosphate,** which is a substance important in the process of bone mineralization and making bones stronger.
[2] **PLP** stands for **pyridoxal 5'-phosphate,** also known as vitamin B6.
[3] This refers to the percentage of the distance a healthy person of similar age, gender, and height would be expected to walk in 6 minutes.

NOTES

COURAGE STARTS WITH STRENSIQ® (asfotase alfa)

Now that you're empowered with a diagnosis, you're ready to take charge of your treatment. Fear of injection is natural. Alexion provides educational materials and programs, support communities and resources, plus the encouragement to keep you going strong.

The STRENSIQ Starter Kit includes the information you need to successfully begin and stay on treatment. You'll be given access to a wealth of Alexion resources and support. In this kit you'll find what you need to confidently start your journey with STRENSIQ:

- **OneSource™ Brochure:** An overview of services provided by your OneSource Case Manager
- **STRENSIQ Patient Brochure:** Detailed information on how STRENSIQ works and what to expect while taking treatment
- **STRENSIQ Patient Journal and Symptom Tracker:** Use this journal to track your symptoms and prepare for doctors' visits
- **Medical Alert Card:** Carry this wallet-sized card with you to inform healthcare providers and lab personnel of your condition and potential lab assay interference while being treated with STRENSIQ
- **Patient Education Event Card:** Find out more about how to engage in HPP Educational Events

As you review these materials, remember that you can always call 1-888-765-4747 to talk with a OneSource Case Manager.

TEAR HERE

Strensiq® (asfotase alfa) For injection | 40 mg/mL

STARTING STRENSIQ®

Have you just been prescribed STRENSIQ and you're not sure where to start?

The STRENSIQ Starter Kit is a great resource for the information you will need to start taking STRENSIQ.

Requesting your STRENSIQ Starter Kit is as easy as calling 1-888-765-4747 or emailing OneSource@alexion.com.

WHAT'S IN YOUR STRENSIQ STARTER KIT

Your STRENSIQ Starter Kit will include:

- OneSource™ Brochure
- STRENSIQ Patient Brochure
- STRENSIQ Patient Journal and Symptom Tracker
- Medical Alert Card
- Patient Education Event Card
- STRENSIQ Prescribing Information

If you have any questions, you can call OneSource™ at 1-888-765-4747

ALEXION®

Strensiq® (asfotase alfa) for injection | 40 mg/mL

INJECTION STARTER KIT

The Injection Starter Kit has supplies and information you need to start STRENSIQ® (asfotase alfa) treatment with success. The kit includes:

- **Injection Supplies:** Needles, syringes, alcohol wipes, and other necessary supplies to administer your medication
- **Injection IQ:** Learn tips and best practices for administering STRENSIQ
- **Injection Supplies Mat:** Use this injection mat to keep your injection supplies neat and organized and to remind yourself how to prepare the STRENSIQ injection prior to administration
- **Injection Site Tracker and Calendar:** Use this injection site tracker to help establish a routine that works for you
- **STRENSIQ Travel Requirements Letter:** Bring this letter to notify airline staff of the need to keep STRENSIQ with you in the main cabin when you fly
- **OneSource™ Connection Card:** Sign up for this personalized patient support program

Take the first steps with confidence

- Visit **AlexionOneSource.com/Enrollment-Form** to complete the OneSource Enrollment and Authorization Form. Be sure to check all the boxes on the form to receive additional materials or follow-up communication.
- Talk to your doctor about STRENSIQ
- Get involved in the HPP community and join us for the next **Unmask HPP** Educational Events
- Reach out to self-nominate to become an **HPP STAR** and share your experience

For details, call 1-888-765-4747 or email us at OneSource@alexion.com

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Replace what's missing.
Replace fear with courage.

INDICATION

What is STRENSIQ® (asfotase alfa)?
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SELECT IMPORTANT SAFETY INFROMATION

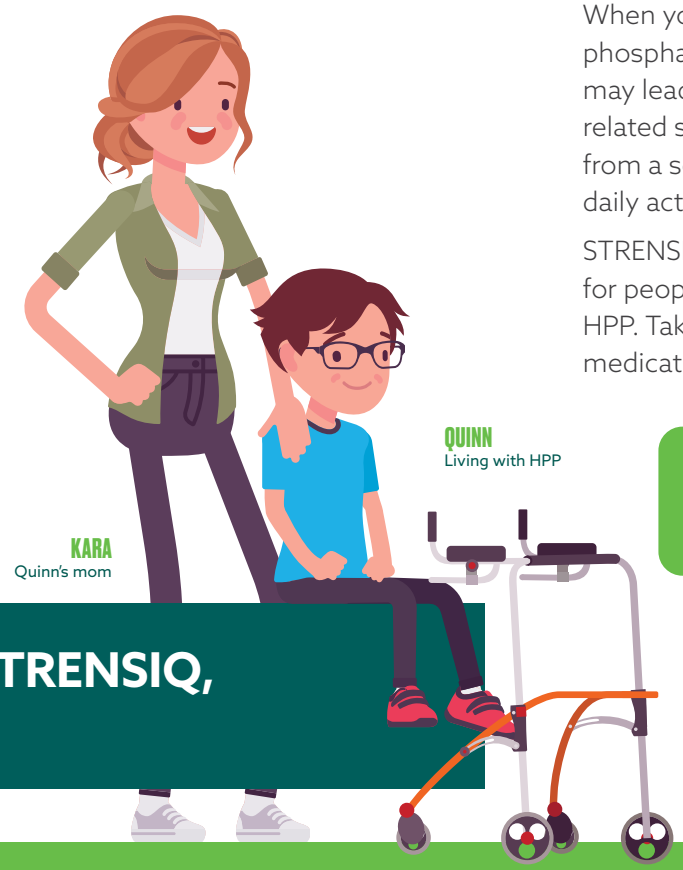
The most common side effects of STRENSIQ include local skin injection-site reactions (red skin patches, bruising, color change, pain, itching, thinning, swelling, pits, and bumps) and calcium buildup in your eyes and kidneys.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

Click here for Patient side

HELP THEM FIND THE COURAGE TO LIVE WITH HYPOPHOSPHATASIA

HPP affects everyone differently and can require coordinating healthcare through a variety of specialists – from endocrinologists and rheumatologists to orthopedists, rehab specialists, dentists, and others. Juggling your loved one's needs may be overwhelming, but when you know the facts about HPP and its treatment, you can help them face their fears head-on and discover courage. Together, you can find hope...and connect with a community that cares.



To learn more about STRENSIQ, visit STRENSIQ.com.

> "Quinn still relies on his mobility support device from time to time, but I am glad that as each day goes on, he is able to have more confidence getting around with his peers."
>
> – Kara, mom of Quinn, living with HPP

Discover Confidence with STRENSIQ® (asfotase alfa)

When your loved one's body lacks sufficient alkaline phosphatase (ALP), they develop weak or "soft" bones, which may lead to skeletal deformities, tooth loss or pain, or other related symptoms. Simple tasks, such as climbing stairs, rising from a seated position, or walking, can become difficult, limiting daily activity.

STRENSIQ is the only ALP enzyme replacement therapy for people with perinatal/infantile-onset and juvenile-onset HPP. Taken at home, STRENSIQ is an injectable prescription medication that provides skeletal healing and improved mobility.

Turn to page 21a to learn more about Starter Kits and other materials offered to those starting STRENSIQ.

Select Important Safety Information

STRENSIQ may cause serious side effects, including serious allergic (hypersensitivity) reactions happened in some people who use STRENSIQ. Stop using STRENSIQ and go to the nearest hospital emergency room right away if you or your loved one have any of the signs and symptoms of a serious allergic reaction, including difficulty breathing, swelling of your eyes, lips, or tongue, hives, feeling faint, nausea or vomiting, dizziness, itching of your lips, tongue, or throat, and choking sensation.

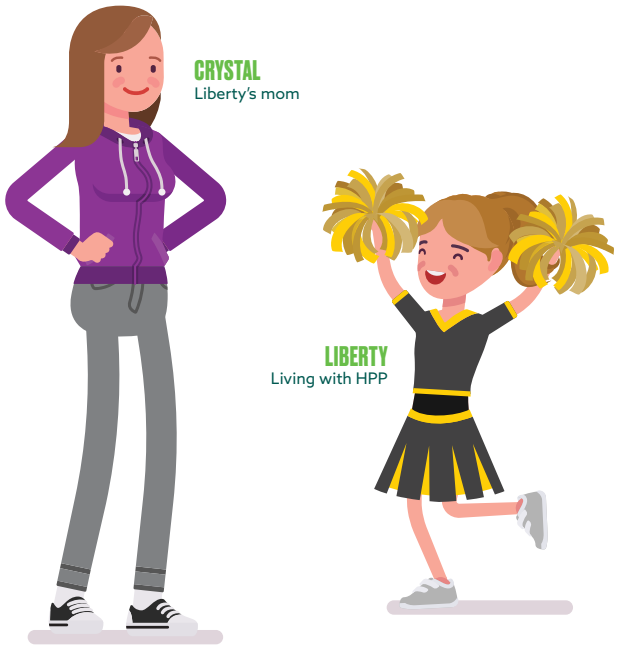
Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

CONFIDENCE BEGINS WITH UNDERSTANDING

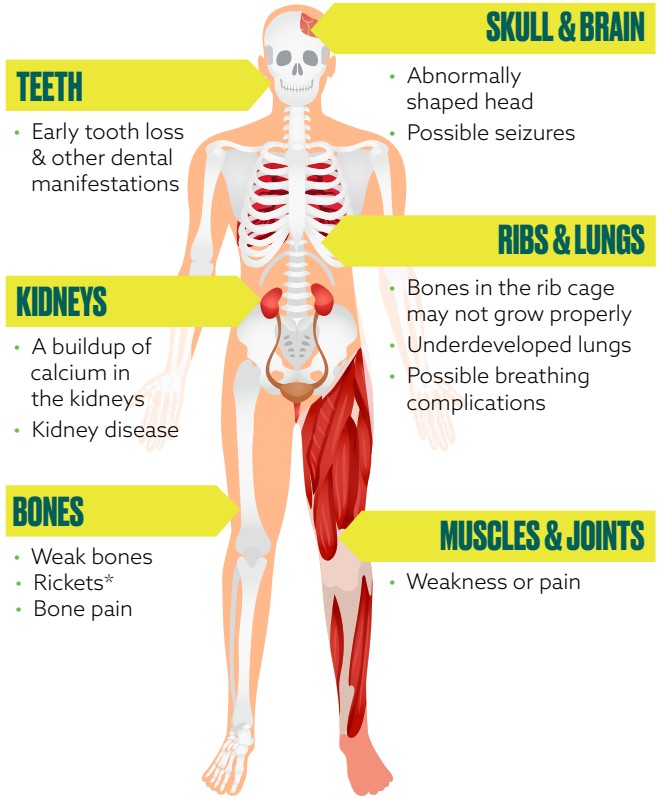
HPP can affect people in different ways. Although it is a bone disease, HPP may impact various areas of the body. In addition, the way HPP makes your loved one feel may vary, and it may affect individuals differently throughout the various phases of development. Understanding the symptoms can give you confidence to help your loved one overcome the physical, social, and emotional challenges.

"HPP doesn't define you. It makes you who you are. With my daughters, I let them know it's okay to be different and never give up on their dreams and goals. Their paths may be different in life, but I tell them to embark on those paths with pride and determination."

– Crystal, mom of Liberty, living with HPP



How does HPP Affect the Body?



This information is for educational purposes only. STRENSIQ® (asfotase alfa) does not address every symptom of HPP listed. Patients must rely on the medical advice of their doctor before seeking any information related to their particular diagnosis, cure or treatment of a condition or disorder. To learn more about STRENSIQ, refer to the Prescribing Information.

* **Rickets** – Decreased bone mineralization.

Select Important Safety Information
STRENSIQ may cause serious side effects, including skin thickening or pits at the injection site (lipodystrophy) has happened several months after using STRENSIQ.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

COURAGEOUS SELF-CARE: WHEN YOU CARE FOR SOMEONE WITH HPP...

As the primary caregiver and advocate for a loved one with HPP, it's common to feel overwhelmed, uncertain, and just plain exhausted. Taking care of yourself is every bit as important as taking care of your loved one. How do you juggle it all? Consider these suggestions for helping yourself and your loved one on your journey together with HPP:

- **Create a tag team:** Ask a friend or family member to learn how to give STRENSIQ® (asfotase alfa) to your loved one so you can enjoy an occasional "night off."
- **Take time for yourself:** Even if it's just an hour a day, set aside some "me time" to relax and unwind. While taking care of your loved one might be your passion, taking time to engage in a favorite hobby or activity will allow you to recharge and unwind so you can continue advocating for the one you love.
- **Talk about it:** Caring for a loved one with a chronic disease can take an emotional toll. Consider speaking to a skilled therapist (or spiritual director at your place of worship) to help you process your feelings and keep going strong.

Turn to page 11a for details about HPP support organizations.

> **"If your loved one has unexplained tooth loss, bone pain, or fatigue, they may have HPP. It is possible to diagnose HPP by just looking at the labs done in the past, such as alkaline phosphatase as a part of the chemistry panel. The good news is that HPP treatment is effective and can really help patients."**
>
> **– HPP Specialist**

STRENSIQ Cares For You

HPP is a rare disease, but you don't have to experience it alone. There is a community of support available to you.

Tap into Resources: OneSource™, a complimentary personalized support program offered by Alexion, provides information and expertise specifically for people with HPP and their caregivers. Call OneSource at 1-888-765-4747 to learn more about HPP and STRENSIQ.

Travel with Confidence: When flying with STRENSIQ, carry the STRENSIQ Travel Requirements Letter with you. This letter can be shown to airline staff to make sure your loved one's STRENSIQ travels with you appropriately. Always travel with STRENSIQ in your carry-on luggage. Do not store STRENSIQ in your checked luggage.

Join us for a complimentary Unmask HPP Educational Events: Hear our HPP STARS share their stories and learn more about STRENSIQ as a treatment option from a healthcare provider. For more information and to register, visit AlexionHPPEvents.com

Select Important Safety Information

STRENSIQ may cause serious side effects, including: Calcium buildup in the eyes and kidneys can occur if you or your loved one have HPP. Your healthcare provider should check the eyes and kidneys while you or your loved one use STRENSIQ. **Decreased efficacy.** Contact your healthcare provider if you or your loved one notice STRENSIQ is no longer working or experience worsening symptoms of HPP (e.g., increased respiratory support, increased difficulty walking, new fractures).

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

DEVELOP A ROUTINE WITH STRENSIQ® (asfotase alfa)

One of the best things you can do for your loved one is to be confident in how and when to administer their medication. In your loved one's first shipment of STRENSIQ, you will receive an Injection Starter Kit. (See page **22a** for a detailed description of what you'll receive.)

Fear-Less Tips for Injecting STRENSIQ

- Carefully read the Patient Information and Instructions for Use before your loved one starts STRENSIQ and each time they get a refill
- Only inject under the skin (subcutaneously) in areas with a substantial amount of fat. STRENSIQ can be injected under the skin of the stomach, buttocks (except in infants), upper arms, or upper legs. Use the Injection Starter Kit for guidance
- Use the Injection IQ: Quick Tips to Prepare for Your Injection booklet to identify injection sites and to administer STRENSIQ
- Use the Injection Site Tracker to record each injection site and rotate between them
- Use the Injection Supplies Mat to keep your loved one's injection materials clean and organized during injections
- Keep up with symptoms between doctors' visits with the STRENSIQ My Treatment Journal & Symptom Tracker
- Always use the exact dose of STRENSIQ prescribed by your loved one's doctor. Before starting STRENSIQ, your loved one's doctor will speak with you about how often STRENSIQ should be injected

"Quinn and I have our STRENSIQ routine. He retrieves the vials while I prepare syringes and supplies. Depending upon the site, either he or I do the injection."

– Kara, mom of Quinn, living with HPP

Get inspired! Go to STRENSIQ.com for tips and other helpful resources.

SPEAK OUT WITH COURAGE

As a caregiver for someone living with HPP, advocating for your loved one becomes a part of daily life. Whether at the doctor's office, at school, or in your neighborhood, being able to effectively communicate about your loved one's condition will help you – and them – stay safe and healthy.

Fear-Less Tips:

- Use the STRENSIQ® (asfotase alfa) Treatment Journal and Symptom Tracker to keep up with HPP issues between appointments. Also, keep an ongoing list of questions for the doctor and bring them to your loved one's next appointment.
- Fill out the Medical Alert Card provided in the Starter Kit and put your loved one's medical information in their mobile device so that essential information about HPP will be with them wherever they are. If you are caring for someone with HPP who attends school/extracurricular activities, please make sure their teachers and coaches are aware of the location of their Medical Alert Card.
- Download information from HPP support groups to share with your child's school administrators, school nurse, and teachers.
- Invite your loved one to develop their own age-appropriate way of describing HPP so they can share their diagnosis with friends and other family members.

"When we received the HPP diagnosis, our pediatrician helped arrange for us to go to a specialty center and meet with a doctor who specialized in HPP. The definitive thing that came out of that trip was a confirmation of the HPP diagnosis. While there, we met another little girl with HPP. It helped our sense of community and increased our support network."

– Becky, mom of Julianna, living with HPP

To learn more about STRENSIQ and HPP, please visit STRENSIQ.com

Select 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 the possible side effects of STRENSIQ. For more information, ask your healthcare provider or pharmacist. Call your healthcare provider for medical advice about side effects. You may report side effects to the US Food and Drug Administration at 1-800-FDA-1088.

Please see STRENSIQ full Prescribing Information, including Patient Information and Instructions for Use.

WHAT'S YOUR BONE IQ?

Test your knowledge of the skeletal system!

1. How many bones are in the human body?
   a. 206 c. 251
   b. 271 d. 312
2. Which contains more bones, the human hand or the foot?
3. What bones are most commonly broken in adults?
4. Which two elements make up 65% of bone?
   a. Bromide & Helium c. Phosphorus & Magnesium
   b. Sodium & Calcium d. Calcium & Phosphorus
5. True or False? Phosphorus is required for all life on Earth.
6. How many people have HPP?
   a. 1 in a million c. 1 in 100,000
   b. 1 in 10,000 d. 1 in 1,000
7. True or False? Teeth are considered bones.
8. Scholars in what country first studied the human skeleton?
   a. Greece c. China
   b. India d. Roman Empire
9. How much weight do bones make up in the body?
   a. 15% c. 30%
   b. 25% d. 45%
10. What is the longest bone in the body?
    a. Tibia c. Femur
    b. Fibula d. Lemur

Quiz answers are on follwing page at the bottom

WALK LIKE AN EGYPTIAN: COULD THIS FAMOUS PHARAOH HAVE HAD HPP?

King Tutankhamun, the famous young Egyptian Pharaoh (1332-1323 BC), is widely known for the treasures discovered in his tomb in the early 20th century. Researchers now believe King Tut may have had HPP!

New research has led to the theory that King Tut may have had hypophosphatasia and provides the first medical explanation for the unusual physiological findings in Tutankhamun and his father Akhenaten, the world's most famous pharaohs.

"Taking into account all the king's other symptoms and injuries, there is no reasonable medical explanation for King Tut to have had Köhler's disease," said Gerald Brandt, an expert on HPP and president of the HPP association in Germany. "A clear cause for the bone problems found in Tutankhamun was missing, and HPP appears to be a likely reason."

Brandt believes that the pharaoh and his family, especially his father Akhenaten, might have suffered from a mild form of HPP based on numerous features of the disease common to HPP.

Source: Softbones.org

Quiz answers: 1: A, 2: Human Hand, 3: Arms, 4: D, 5: True, 6: C, 7: False, 8: B, 9: A, 10: C

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use STRENSIQ safely and effectively. See full prescribing information for STRENSIQ.

STRENSIQ® (asfotase alfa) injection, for subcutaneous use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Dosing and Administration (2.3, 2.4)	6/2020
Warnings and Precautions (5.4)	6/2020

INDICATIONS AND USAGE

STRENSIQ is a tissue nonspecific alkaline phosphatase indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP). (1)

DOSAGE AND ADMINISTRATION

Perinatal/Infantile-Onset HPP (2.1)

- Recommended dosage regimen is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week. Injection site reactions may limit the tolerability of the six times per week regimen.
- The dose may be increased to 3 mg/kg three times per week for insufficient efficacy.

Juvenile-Onset HPP (2.2)

- Recommended dosage regimen is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week. Injection site reactions may limit the tolerability of the six times per week regimen.

Preparation and Weight-Based Dosing (2.3):

- *Caution:* Do not use the 80 mg/0.8 mL vial in pediatric patients weighing less than 40 kg because the systemic asfotase alfa exposure achieved with the 80 mg/0.8 mL vial (higher concentration) is lower than that achieved with the other strength vials (lower concentration). A lower exposure may not be adequate for this subgroup of patients.
- See full prescribing information for tables of weight-based dosing by treatment regimen.

Administration (2.4):

- For subcutaneous injection only.
- Rotate injection sites. Do not administer to areas that are reddened, inflamed or swollen.

DOSAGE FORMS AND STRENGTHS

Injection: 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, or 80 mg/0.8 mL solution in single-dose vials. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Monitor and if a severe reaction occurs, discontinue treatment and initiate appropriate medical treatment. (5.1)
- Lipodystrophy: Localized reactions were reported after several months of treatment; follow proper injection technique and rotate injection sites. (5.2)
- Ectopic Calcifications (eye and kidneys): Monitor using ophthalmologic examinations and renal ultrasounds at baseline and periodically during treatment. (5.3)
- Possible Immune-Mediated Clinical Effects: Evaluate patients for antibody formation if clinically indicated. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (≥ 10%) are injection site reactions, lipodystrophy, ectopic calcifications and hypersensitivity reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drug Interference with Laboratory Tests: Alkaline Phosphatase (ALP) is used as a detection reagent in many laboratory tests and the presence of asfotase alfa in clinical laboratory samples could result in erroneous test results. Inform laboratory personnel and discuss use of an alternative testing platform for patients on treatment. (7.1)
- Serum Alkaline Phosphatase: Serum ALP measurements are expected to be elevated during treatment and may be unreliable for clinical decision making. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STRENSIQ® is indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Perinatal/Infantile-Onset HPP

The recommended dosage regimen of STRENSIQ for the treatment of perinatal/infantile-onset HPP is 6 mg/kg per week administered subcutaneously as either:

- 2 mg/kg three times per week, or
- 1 mg/kg six times per week. Injection site reactions may limit the tolerability of the six times per week regimen *[see Adverse Reactions (6.1)]*.

The dose of STRENSIQ may be increased for lack of efficacy (e.g., no improvement in respiratory status, growth, or radiographic findings) up to 9 mg/kg per week administered subcutaneously as 3 mg/kg three times per week.

2.2 Dosage for Juvenile-Onset HPP

The recommended dosage regimen of STRENSIQ for the treatment of juvenile-onset HPP is 6 mg/kg per week administered subcutaneously as either:

- 2 mg/kg three times per week, or
- 1 mg/kg six times per week. Injection site reactions may limit the tolerability of the six times per week regimen *[see Adverse Reactions (6.1)]*.

2.3 Preparation and Weight-Based Dosing Tables

Caution: Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg because the systemic exposure of asfotase alfa achieved with the 80 mg/0.8 mL vial (higher concentration) is lower than that achieved with the other strength vials (lower concentration). A lower exposure may not be adequate for this subgroup of patients *[see Dosage Forms and Strengths (3), Clinical Pharmacology (12.3)]*.

1. Determine the total weekly volume needed for the prescribed dosage based on the patient's weight and recommended dosage. Follow these steps to determine the patient dose.

   Total weekly dose (mg) = patient's weight (kg) x prescribed dose (mg/kg/week)

Total injection volume (mL) per week = Total dose (mg/week) divided by the STRENSIQ concentration (40 mg/mL or 100 mg/mL). Note product concentrations are: 40 mg/mL (vial strengths 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL) or 100 mg/mL (vial strength 80 mg/0.8 mL).

Round total injection volume to the nearest hundredth of a mL

Total number of vials per week = Total injection volume divided by vial volume (mL)

2. Determine the number of injection days per week (three or six per week).

3. Determine dose per injection day. Patient weights should be rounded to the nearest kilogram when determining dose. Use the following tables for guidance, for patients administering 2 mg/kg three times per week (Table 1), 1 mg/kg six times per week (Table 2) and for dose escalations to 3 mg/kg three times per week, recommended only for patients with perinatal/infantile-onset HPP *[see Dosage and Administration (2.1)]* (Table 3).

Table 1: Weight-Based Dosing for Administration of 2 mg/kg Three Times per Week

Body Weight (kg)*	Dose to Inject	Volume to Inject	Vial Configuration
3	6 mg	0.15 mL	18 mg/0.45 mL
4	8 mg	0.2 mL	18 mg/0.45 mL
5	10 mg	0.25 mL	18 mg/0.45 mL
6	12 mg	0.3 mL	18 mg/0.45 mL
7	14 mg	0.35 mL	18 mg/0.45 mL
8	16 mg	0.4 mL	18 mg/0.45 mL
9	18 mg	0.45 mL	18 mg/0.45 mL
10	20 mg	0.5 mL	28 mg/0.7 mL
15	30 mg	0.75 mL	40 mg/1 mL
20	40 mg	1 mL	40 mg/1 mL
25	50 mg	1.25 mL	Two 28 mg/0.7 mL vials
30	60 mg	1.5 mL	Two 40 mg/1 mL vials
35	70 mg	1.75 mL	Two 40 mg/1 mL vials
40	80 mg	0.8 mL	80 mg/0.8 mL
50	100 mg	1 mL	Two 80 mg/0.8 mL vials
60	120 mg	1.2 mL**	Two 80 mg/0.8 mL vials
70	140 mg	1.4 mL**	Two 80 mg/0.8 mL vials
80	160 mg	1.6 mL**	Two 80 mg/0.8 mL vials

* Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg *[see Clinical Pharmacology (12.3)]*.

** When preparing a volume for injection greater than 1 mL, split the volume equally between two syringes, and administer two injections. When administering the two injections, use two separate injection sites.

Table 2: Weight-Based Dosing for Administration of 1 mg/kg Six Times per Week

Body Weight (kg)*	Dose to Inject	Volume to Inject	Vial Configuration
3	3 mg	0.08 mL	18 mg/0.45 mL
4	4 mg	0.1 mL	18 mg/0.45 mL
5	5 mg	0.13 mL	18 mg/0.45 mL
6	6 mg	0.15 mL	18 mg/0.45 mL
7	7 mg	0.18 mL	18 mg/0.45 mL
8	8 mg	0.2 mL	18 mg/0.45 mL
9	9 mg	0.23 mL	18 mg/0.45 mL
10	10 mg	0.25 mL	18 mg/0.45 mL
15	15 mg	0.38 mL	18 mg/0.45 mL
20	20 mg	0.5 mL	28 mg/0.7 mL
25	25 mg	0.63 mL	28 mg/0.7 mL
30	30 mg	0.75 mL	40 mg/1 mL
35	35 mg	0.88 mL	40 mg/1 mL
40	40 mg	1 mL	40 mg/1 mL
50	50 mg	0.5 mL	80 mg/0.8 mL
60	60 mg	0.6 mL	80 mg/0.8 mL
70	70 mg	0.7 mL	80 mg/0.8 mL
80	80 mg	0.8 mL	80 mg/0.8 mL
90	90 mg	0.9 mL	Two 80 mg/0.8 mL vials
100	100 mg	1 mL	Two 80 mg/0.8 mL vials

* Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg *[see Clinical Pharmacology (12.3)]*.

Table 3: Weight-Based Dosing for Administration of 3 mg/kg Three Times per Week – Only for Perinatal/Infantile-Onset HPP*

Body Weight (kg)**	Dose to Inject	Volume to Inject	Vial Configuration
3	9 mg	0.23 mL	18 mg/0.45 mL
4	12 mg	0.3 mL	18 mg/0.45 mL
5	15 mg	0.38 mL	18 mg/0.45 mL
6	18 mg	0.45 mL	18 mg/0.45 mL
7	21 mg	0.53 mL	28 mg/0.7 mL
8	24 mg	0.6 mL	28 mg/0.7 mL
9	27 mg	0.68 mL	28 mg/0.7 mL
10	30 mg	0.75 mL	40 mg/1 mL
15	45 mg	1.13 mL***	Two 28 mg/0.7 mL vials
20	60 mg	1.5 mL***	Two 40 mg/1 mL vials
25	75 mg	1.88 mL***	Two 40 mg/1 mL vials

* A regimen of 3 mg/kg three times per week is recommended only for patients with perinatal/infantile-onset HPP *[see Dosage and Administration (2.1)]*

** Do not use the 80 mg/0.8 mL vial of STRENSIQ in pediatric patients weighing less than 40 kg *[see Clinical Pharmacology (12.3)]*.

*** When preparing a volume for injection greater than 1 mL, split the volume equally between two syringes, and administer two injections. When administering the two injections, use two separate injection sites.

4. Take the unopened STRENSIQ vial(s) out of the refrigerator 15 to 30 minutes before injecting to allow the liquid to reach room temperature.

Do not warm STRENSIQ in any other way (for example, do not warm it in a microwave or in hot water).

5. Inspect the solution in the vial(s) for particulate matter and discoloration. STRENSIQ is supplied as a clear, slightly opalescent or opalescent, colorless to slightly yellow aqueous solution; a few small translucent or white particles may be present. Discard any vial(s) not consistent with this appearance.
6. Assemble injection supplies. Administer STRENSIQ using sterile disposable 1 mL syringes and ½ inch injection needles, between 25 to 29 gauge are recommended. The use of two different gauge needles is recommended, a larger bore needle (e.g. 25 gauge) for withdrawal of the medication, and a smaller bore needle (e.g. 29 gauge) for the injection. For doses greater than 1 mL, the injection volume should be split equally between two 1 mL syringes. Always use a new syringe and needle for each injection.
7. Remove vial cap, aseptically prepare the vial and insert the syringe into the vial to withdraw the prescribed dose for administration. Do not shake.
8. Remove any air bubbles in the syringe and verify the correct dose.
9. STRENSIQ vials are for one time use only. Discard any unused product.

2.4 Administration

STRENSIQ is for subcutaneous injection only.

- When administering two injections, use two separate injection sites.
- Administer STRENSIQ within 3 hours upon removal of the vial(s) from refrigeration.
- Rotate the injection from among the following sites to reduce the risk of lipodystrophy: abdominal area, thigh, deltoid, or buttocks *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*.
- Do NOT administer injections in areas that are reddened, inflamed, or swollen.
- Inject STRENSIQ subcutaneously into the determined site and properly dispose of the syringe and the needle.

3 DOSAGE FORMS AND STRENGTHS

STRENSIQ is a clear, slightly opalescent or opalescent, colorless to slightly yellow aqueous solution; few small translucent or white particles may be present. The product is available as:

- Injection: 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, or 80 mg/0.8 mL solution in single-dose vials

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have been reported in STRENSIQ-treated patients. Signs and symptoms consistent with anaphylaxis included difficulty breathing, choking sensation, nausea, periorbital edema, and dizziness. These reactions have occurred within minutes after subcutaneous administration of STRENSIQ and have been observed more than 1 year after treatment initiation. Other hypersensitivity reactions have also been reported in STRENSIQ-treated patients, including vomiting, fever, headache, flushing, irritability, chills, erythema, rash, pruritus and oral hypoesthesia *[see Adverse Reactions (6.1)]*.

If a severe hypersensitivity reaction occurs, discontinue STRENSIQ treatment and initiate appropriate medical treatment. Consider the risks and benefits of re-administering STRENSIQ to individual patients following a severe reaction. If the decision is made to re-administer the product, monitor patients for a reoccurrence of signs and symptoms of a severe hypersensitivity reaction.

5.2 Lipodystrophy

Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with STRENSIQ in clinical trials *[see Adverse Reactions (6.1)]*. Advise patients to follow proper injection technique and to rotate injection sites *[see Dosage and Administration (2.4)]*.

5.3 Ectopic Calcifications

Patients with HPP are at increased risk for developing ectopic calcifications. Events of ectopic calcification, including ophthalmic (conjunctival and corneal) and renal (nephrocalcinosis, nephrolithiasis), have been reported in the clinical trial experience with STRENSIQ. There was insufficient information to determine whether or not the reported events were consistent with the disease or due to STRENSIQ. No visual changes or changes in renal function were reported resulting from the occurrence of ectopic calcifications.

Ophthalmology examinations and renal ultrasounds are recommended at baseline and periodically during treatment with STRENSIQ to monitor for signs and symptoms of ophthalmic and renal ectopic calcifications and for changes in vision or renal function.

5.4 Possible Immune-Mediated Clinical Effects

In clinical trials, most STRENSIQ-treated patients developed anti-asfotase alfa antibodies and neutralizing antibodies which resulted in reduced systemic exposure of asfotase alfa *[see Immunogenicity (6.2)]*. In postmarketing reports, some STRENSIQ-treated patients

with initial therapeutic response subsequently developed recurrence and worsening in disease-associated laboratory and radiographic biomarkers (some in association with neutralizing antibodies) suggesting possible immune-mediated effects on STRENSIQ's pharmacologic action resulting in disease progression *[see Adverse Reactions (6.3)]*. The effect of anti-asfotase alfa antibody formation on the long-term efficacy of STRENSIQ is unknown. There are no marketed anti-asfotase alfa antibody tests. If patients experience progression of HPP symptoms or worsening of disease-associated laboratory and imaging biomarkers after a period of initial therapeutic response to STRENSIQ, consider obtaining anti-asfotase alfa antibody testing by contacting STRENSIQ Medical Information at Alexion at 1-888-765-4747 or by email at medinfo@alexion.com. Close clinical follow up is recommended.

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Lipodystrophy *[see Warnings and Precautions (5.2)]*
- Ectopic Calcifications *[see Warnings and Precautions (5.3)]*
- Possible Immune-Mediated Clinical Effects *[see Warnings and Precautions (5.4)]*

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 practice.

The data described below reflect exposure to STRENSIQ in 99 patients with perinatal/infantile- or juvenile onset HPP (age 1 day to 58 years) treated with STRENSIQ, most for more than 2 years (range 1 day to 312 weeks [78 months]): 51 patients received at least 96 weeks (24 months) of treatment and 39 patients received 168 weeks (42 months) or more of treatment *[see Clinical Studies (14)]*.

Common Adverse Reactions

Overall, the most common adverse reactions reported were injection site reactions (63%). Other common adverse reactions included lipodystrophy (28%), ectopic calcifications (14%), and hypersensitivity reactions (12%).

Table 4 summarizes the adverse reactions that occurred at a rate of at least 10% in clinical trials following subcutaneous injection of STRENSIQ by patient population and STRENSIQ dosage regimen.

The frequency of injection site reactions, lipodystrophy and ectopic calcification were higher in patients with juvenile-onset HPP as compared to perinatal/infantile-onset HPP patients.

The majority of injection site reactions resolved within a week. Two patients experienced injection site reactions that led to reductions of their STRENSIQ dose. One patient switched from six times per week dosing to 3 times per week dosing as a result of injection site reactions. One other patient experienced a severe injection site reaction of injection site discoloration and withdrew from the trial.

Table 4: Adverse Reactions Reported in at Least 10% of Patients with Perinatal/Infantile- or Juvenile-onset HPP Enrolled in STRENSIQ Clinical Trials

	Perinatal/ Infantile-onset HPP			Juvenile-onset HPP
Adverse Reaction Category or Term	**STRENSIQ less than or equal to 6 mg/kg per week (N=66) n (%)**	**STRENSIQ more than 6 mg/kg/week[a] (N=13) n (%)**	**Total (N=79) n (%)**	**STRENSIQ (N=20) n (%)**
Injection site reactions	38 (58)	6 (46)	44 (56)	18 (90)
Erythema	29 (44)	3 (23)	32 (41)	15 (75)
Discoloration/ Hypopigmentation	11 (17)	1 (8)	12 (15)	8 (40)
Pain/ Tenderness	10 (15)	1 (8)	11 (14)	8 (40)
Pruritus/ Itching	10 (15)	0 (0)	10 (13)	7 (35)
Swelling	8 (12)	0 (0)	8 (10)	6 (30)
Induration	9 (14)	1 (8)	10 (13)	3 (15)
Macule	4 (6)	0 (0)	4 (5)	7 (35)
Reaction, not otherwise specified	6 (9)	1 (8)	7 (9)	4 (20)
Bruising	6 (9)	0 (0)	6 (8)	4 (20)
Nodule	2 (3)	0 (0)	2 (3)	2 (10)
Other injection site reactions[b]	10 (15)	3 (23)	13 (17)	4 (20)
Ectopic calcifications	3 (5)	0 (0)	3 (4)	11 (55)
Lipodystrophy	12 (18)	2 (15)	14 (18)	14 (70)
Injection site atrophy	4 (6)	2 (15)	6 (8)	8 (40)
Injection site hypertrophy	5 (8)	0 (0)	5 (6)	6 (30)
Other lipodystrophy[c]	4 (6)	0 (0)	4 (5)	1 (5)
Hypersensitivity reactions	7 (11)	3 (23)	10 (13)	2 (10)
Vomiting/emesis	2 (3)	2 (15)	4 (5)	2 (10)
Other hypersensitivity reactions[d]	6 (9)	2 (15)	8 (10)	2 (10)

[a] Adverse reactions are from the combined period of 6 mg/kg and above (i.e. total drug exposure regardless of starting dose and intermediary doses as long as the patient reached doses > 6 mg/kg)

[b] Other injection site reactions include injection site rash, inflammation, papule, hemorrhage, hematoma, urticaria, warmth, calcification, mass, scar and cellulitis.

[c] Other lipodystrophy includes lipohypertrophy.

[d] Other hypersensitivity reactions include erythema/redness, pyrexia/fever, irritability, nausea, pain, rigor/chills, hypoesthesia oral, headache, flushing, and anaphylaxis.

Less Common Adverse Reactions

Adverse reactions that occurred at rates less than 1% included:

- Hypocalcemia
- Renal Stones
- Chronic hepatitis
- Decreased vitamin B6

Long-Term Safety

In long-term extension trials reflecting a median exposure to STRENSIQ of 142 weeks (range 0.1 weeks to 392 weeks) in 112 patients with perinatal/infantile- (n = 89), juvenile- (n = 22), and adult-onset (n = 1) HPP (age at enrollment = 1 day to 66.5 years), the most common adverse reactions were similar to those reported in Table 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. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay 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 the antibodies in the studies described below with the incidence of antibodies in other studies or to other asfotase alfa products may be misleading.

During clinical trials, anti-asfotase alfa antibodies have been detected in patients receiving treatment with STRENSIQ using an electrochemiluminescent (ECL) immunoassay. Antibody positive samples were tested to determine the presence of neutralizing antibodies based on in vitro inhibition of the catalytic activity of STRENSIQ.

Among STRENSIQ-treated patients with hypophosphatasia (HPP) in clinical studies who had post-baseline antibody data available, 97/109 (89%) tested positive for anti-asfotase alfa antibodies at some time point during STRENSIQ treatment. Among those 97 patients, 55 (57%) also tested positive for neutralizing antibodies at some time point during STRENSIQ treatment. No correlation was observed between the anti-asfotase alfa antibody titers and the neutralizing antibody (% inhibition) values. Formation of anti-asfotase alfa antibody resulted in a reduced systemic exposure of asfotase alfa *[see Clinical Pharmacology (12.3)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of STRENSIQ. Because these reactions are reported voluntarily from a population of

uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Some STRENSIQ-treated patients with initial therapeutic response to STRENSIQ subsequently developed worsening in disease-associated laboratory and radiographic biomarkers (some in association with neutralizing antibodies) suggesting possible immune-mediated effects on STRENSIQ's pharmacologic action resulting in disease progression *[see Warnings and Precautions (5.4)]*.

7 DRUG INTERACTIONS

7.1 Drug Interference with Laboratory Tests

Laboratory Tests Utilizing Alkaline Phosphatase as a Detection Reagent

Studies have shown that there is analytical interference between asfotase alfa and laboratory tests that utilize an alkaline phosphatase (ALP)-conjugated test system, rendering erroneous test results in patients treated with STRENSIQ. ALP-conjugated test systems are utilized to measure substances such as hormones, bacterial antigens and antibodies. Therefore, it is recommended that laboratory assays which do not have ALP-conjugate technology be used when testing samples from patients who are receiving STRENSIQ.

To avoid erroneous test results for patients treated with STRENSIQ, inform laboratory personnel that the patient is being treated with STRENSIQ and discuss the use of a testing platform which does not utilize an ALP-conjugated test system.

Serum Alkaline Phosphatase

High serum ALP measurements detected through clinical laboratory testing are expected in patients receiving STRENSIQ and reflect circulating concentrations of asfotase alfa**.**

Do not rely on serum ALP measurements for clinical decision making in patients treated with STRENSIQ.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on STRENSIQ use in pregnant women to inform a drug associated risk. In animal reproduction studies, asfotase alfa administered intravenously to pregnant rats and rabbits during the period of organogenesis showed no evidence of fetotoxicity, embryolethality or teratogenicity at doses causing plasma exposures up to 21 and 24 times, respectively, the exposure at the recommended human dose *(see Data)*.

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.

Data

Animal Data

Asfotase alfa administered during the period of organogenesis to rats (from gestation Day 6 to Day 19 post-partum) and rabbits (on gestation days 7 to 19) at intravenous doses up to 50 mg/kg/day, approximately 21 and 24 times the human AUC of 65486 ng.h/mL at 2 mg/kg dose administered three times weekly for a 50 kg individual, respectively did not cause any adverse effects on embryofetal development. A pre- and post-natal development study in pregnant rats showed no evidence of adverse effects on pre- and post-natal development at intravenous doses (from Day 6 of gestation to Day 19 postpartum) of asfotase alfa up to 50 mg/kg/day approximately 21 times the human AUC of 65486 ng.h/mL at 2 mg/kg dose administered three times weekly for a 50 kg individual.

8.2 Lactation

Risk Summary

There are no data on the presence of asfotase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STRENSIQ and any potential adverse effects on the breastfed infant from asfotase alfa or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of STRENSIQ for the treatment of perinatal/infantile- and juvenile-onset HPP have been established in pediatric patients. Use of STRENSIQ for this indication is based on 4 prospective, open-label clinical trials conducted in 89 pediatric patients with perinatal/infantile-onset or juvenile-onset HPP *[see Clinical Studies (14)]*.

8.5 Geriatric Use

No patients with perinatal/infantile- or juvenile-onset HPP aged 65 years were enrolled in clinical trials of STRENSIQ. Therefore, there is no information available to determine whether patients aged 65 years and over respond differently from younger patients.

11 DESCRIPTION

Asfotase alfa is a tissue nonspecific alkaline phosphatase (TNSALP) produced by recombinant DNA technology in a Chinese hamster ovary cell line. Asfotase alfa is a soluble glycoprotein composed of two identical polypeptide chains. Each chain contains 726 amino acids with a theoretical mass of 161 kDa. Each chain consists of the catalytic domain of human TNSALP, the human immunoglobulin G_1 Fc domain and a deca-aspartate peptide used as a bone targeting domain. The two polypeptide chains are covalently linked by two disulfide bonds.

STRENSIQ (asfotase alfa) injection is a sterile, preservative-free, nonpyrogenic, clear, slightly opalescent or opalescent, colorless to slightly yellow, with few small translucent or white particles, aqueous solution for subcutaneous administration. STRENSIQ is supplied in glass single-dose vials containing asfotase alfa; dibasic sodium phosphate, heptahydrate; monobasic sodium phosphate, monohydrate; and sodium chloride at a pH between 7.2 and 7.6. Table 5 describes the content of STRENSIQ vial presentations.

Table 5: Content of STRENSIQ Vial Presentations

Ingredient	**Quantity per Vial**			
Asfotase Alfa	18 mg/0.45 mL	28 mg/0.7 mL	40 mg/mL	80 mg/0.8 mL
Dibasic sodium phosphate, heptahydrate	2.48 mg	3.85 mg	5.5 mg	4.4 mg
Monobasic sodium phosphate, monohydrate	0.28 mg	0.43 mg	0.62 mg	0.5 mg
Sodium chloride	3.94 mg	6.13 mg	8.76 mg	7.01 mg

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HPP is caused by a deficiency in TNSALP enzyme activity, which leads to elevations in several TNSALP substrates, including inorganic pyrophosphate (PPi). TNSALP is a metallo-enzyme that catalyzes the hydrolysis of phosphomonoesters with release of inorganic phosphate and alcohol. Elevated extracellular levels of PPi block hydroxyapatite crystal growth which inhibits bone mineralization and causes an accumulation of unmineralized bone matrix which manifests as rickets and bone deformation in infants and children and as osteomalacia (softening of bones) once growth plates close, along with muscle weakness. Replacement of the TNSALP enzyme upon STRENSIQ treatment reduces the enzyme substrate levels.

12.2 Pharmacodynamics

Perinatal/infantile- and juvenile-onset HPP patients treated with STRENSIQ had reductions in plasma TNSALP substrates, PPi and pyridoxal 5'-phosphate (PLP) within 6 to 12 weeks of treatment. Reductions in plasma PPi and PLP levels did not correlate with clinical outcomes.

Bone biopsy data from perinatal/infantile-onset and juvenile-onset HPP patients treated with STRENSIQ demonstrated decreases in osteoid volume and thickness indicating improved bone mineralization.

12.3 Pharmacokinetics

Based on data in 38 HPP patients, the pharmacokinetics of asfotase alfa exhibit dose proportionality across the dose range of 0.3 mg/kg to 3 mg/kg once every other day (three times a week) and appear to be time-independent. Steady state exposure was achieved as

early as three weeks after the administration of the first dose. The elimination half-life following subcutaneous administration was approximately 5 days.

Table 6 summarizes the pharmacokinetic parameters following multiple doses in 20 HPP patients after subcutaneous administration of STRENSIQ at 2 mg/kg three times per week in Study 2 (age of less than or equal to 5 years) and Study 3 (age of greater than 5 to 12 years), indicating the pharmacokinetics were similar between patients in the two age groups.

Table 6: Summary of Pharmacokinetic Parameters Following Multiple Subcutaneous Administration of STRENSIQ 2 mg/kg Three Times per Week

	Study 2	**Study 3**
N	14	6
Age (year)	3.4 ± 2.1 (0.2, 6.2)	8.6 ± 2.2 (6.1, 12.6)
Weight at baseline (kg)	11.2 ± 5.0 (2.9, 17.1)	21.2 ± 7.9 (11.4, 35.4)
t_{last} (h)	48.1 ± 0.1 (47.9, 48.3)	48.0 ± 0.1 (48.0, 48.1)
t_{max} (h)	14.9 ± 10.4 (0, 32.2)	20.8 ± 10.0 (11.9, 32.2)
C_{max} (ng/mL)	1794 ± 690 (856, 3510)	2108 ± 788 (905, 3390)
AUC_t (h*ng/mL)	66042 ± 25758 (27770, 119122)	89877 ± 33248 (37364, 142265)
Accumulation Ratio[a]	1.5	3.9

[a] Ratio values reflect the fold increase of AUC_t from Week 1 based on mean AUC_t, values.
Data are presented as mean ± standard deviation (range). Study 3 includes patients with perinatal/infantile- or juvenile-onset of disease. t_{last}, time of last concentration; t_{max}, time of maximal concentration; C_{max}, maximal concentration; AUC_t, area under the concentration-time curves over a dosing interval of 48 hours

Population PK analysis of asfotase alfa concentrations supports weight-based dosing because body weight is a major covariate of asfotase alfa clearance. The formulation concentration had an impact on the systemic exposure of asfotase alfa in HPP patients. The higher concentration formulation (80 mg/0.8 mL vial) achieved an approximately 25% lower systemic asfotase alfa exposure (i.e., concentrations and AUC) compared to the lower concentration formulations (18 mg/0.45 mL, 28 mg/0.7 mL or 40 mg/mL vials) at the same dose of STRENSIQ *[see Dosage and Administration (2.1)]*.

Anti-Drug Antibody Effects on Pharmacokinetics

Formation of anti-drug antibodies resulted in reduced systemic exposure of asfotase alfa.

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 asfotase alfa. Asfotase alfa at intravenous doses up to 50 mg/kg/day administered daily in pregnant rats (approximately 21 times the human AUC of 65486 ng.h/mL at 2 mg/kg dose administered three times weekly for a 50 kg individual) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Perinatal/Infantile-Onset HPP

Study 1 was a 24-week prospective single-arm trial in 11 patients with severe perinatal/infantile-onset HPP. In this study, 7/11 (64%) were female and 10/11 (91%) patients were white, and age ranged from 3 weeks to 39.5 months. Severe perinatal/infantile-onset HPP was defined as biochemical, medical history and radiographic evidence of HPP as well as the presence of any of the following: rachitic chest deformity, vitamin B6-dependent seizures, or failure to thrive. Ten of 11 patients completed the 24-week trial and continued treatment in the extension phase. Nine patients have been treated for at least 216 weeks (54 months) and 4 patients have been treated for over 240 weeks (60 months). Patients received subcutaneous STRENSIQ 3 mg/kg per week for the first month; subsequently, dose increases up to 9 mg/kg per week were allowed for changes in weight and/or for lack of efficacy. All 10 patients required dose increases up to 6 mg/kg per week or higher; 9 patients increased between 4 and 24 weeks after starting treatment and 1 patient increased after 70 weeks due to suboptimal clinical response. One patient's dose was decreased from 9 mg/kg per week to 6 mg/kg per week based on PK data.

Study 2 was a prospective open-label study in 59 patients with perinatal/infantile-onset HPP. In this study, 32/59 (54%) were female, 46/59 (78%) were white, and age ranged from 1 day to 78 months. Patients received subcutaneous STRENSIQ at 6 mg/kg per week for the first 4 weeks. Ten patients received dose increases higher than 6 mg/kg per week due to suboptimal clinical response, with dose increases occurring between 8 and 24 weeks after starting treatment. The recommended dosage regimen of STRENSIQ for the treatment of perinatal/infantile-onset HPP is up to 9 mg/kg per week administered subcutaneously as 3 mg/kg three times per week *[see Dosage and Administration (2.1)]*.

Forty-one patients were treated for at least 24 weeks (6 months) and 15 patients were treated for at least 96 weeks (24 months).

Survival and Ventilation-Free Survival in Perinatal/Infantile-Onset HPP

Survival and invasive ventilation-free survival were compared in STRENSIQ-treated patients (Studies 1 and 2) with a historical cohort of untreated patients with similar clinical characteristics (Table 7 and Figure 1).

Table 7: Survival and Invasive Ventilation-Free Survival in STRENSIQ-Treated versus Historical Control Patients with Perinatal/ Infantile-Onset HPP (Pooled Studies 1 and 2)

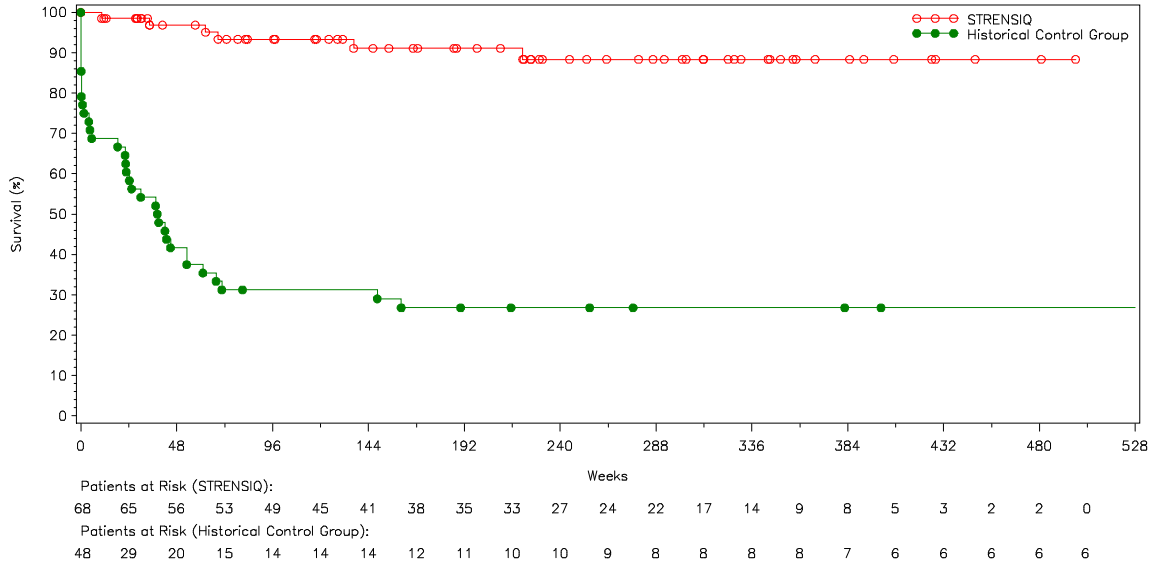
	STRENSIQ-Treated	**Historical Controls**
Survival	n = 68	n = 48
Alive at Point of Last Contact (%)	91	27
Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.14 (0.05, 0.39)	
Kaplan-Meier Estimate and Alive at Age 1 Year (Week 48) (%)	97	42
Invasive Ventilation-Free Survival**	n = 54	n = 48
Alive and Not on Ventilation at Point of Last Contact (%)	85	25
Hazard Ratio (STRENSIQ/Historical Control), 95% Confidence Interval*	0.21 (0.09, 0.51)	
Kaplan-Meier Estimate of Alive and Not on Ventilation at Age 1 Year (Week 48) (%)	96	31

* Adjusted for year of diagnosis.

** Alive and not initiating invasive ventilation after start of STRENSIQ treatment. STRENSIQ-treated patients on invasive ventilation at baseline were excluded from this analysis.

In patients who required any form of respiratory support, 21 of 26 (81%) of the treated patients survived through their last assessment (median age at last assessment was 3.2 years of age), versus 1 of 20 (5%) of historical controls.

Figure 1: Overall Survival in STRENSIQ-Treated versus Historical Control Patients with Perinatal/ Infantile-Onset HPP (Pooled Studies 1 and 2)



x-axis truncated at Week 528; there were 6 historical control patients censored after truncation with censored times ranging from 538 to 1030 weeks

Skeletal Manifestations in Perinatal/Infantile-Onset HPP

Radiographs from 68 STRENSIQ-treated perinatal/infantile-onset HPP patients, including 64 patients in Studies 1 and 2, and 4 patients in Study 3 *[see Clinical Studies (14.2)]*, were examined to assess HPP-related rickets using the 7-point Radiographic Global Impression of Change (RGI-C) scale. Patients with a minimum RGI-C score of +2 were defined as "responders". Radiologic improvements could be seen by Month 24; at last assessment, 50/68 [74%] treated patients were rated as RGI-C responders. No comparative data were available from historical controls. The mean time interval between the baseline and last RGI-C assessment was 24 months (range was 1 month to 67 months).

Eighteen perinatal/infantile-onset HPP patients experienced fractures during the course of treatment. There were insufficient data to determine the effect of STRENSIQ on fractures.

Growth in Perinatal/Infantile-Onset HPP

Height and weight measurements (as measured by Z-scores) were available post-treatment for 72 perinatal/infantile-onset HPP patients, including 68 patients enrolled in Studies 1 and 2, and 4 patients enrolled in Study 3 (Table 8).

Table 8: Perinatal/Infantile-Onset Height and Weight Measurements as Measured by Z-Score (Studies 1 and 2)

	Height Z-score				Weight Z-score			
	Baseline		Last Assessment		Baseline		Last Assessment	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
Studies 1 and 2* (N=68)	-3.3	-10.1, 0.9	-2.9	-10.6, 0.4	-3.2	-23.8, 0	-2.4	-20.9. 1.1
Study 3 (N=4)**	-2.6	-6.6, -0.7	-1.5	-5.8, 0.4	-2.5	-8.2, -1.0	-1.5	-5.4, 0.5

*The mean time interval between baseline and last assessment was 21 months (range was 1 month to 72 months).
**The mean time between baseline and last assessment was 56 months (range was 53 months to 60 months).

Long-Term Extension Trials in Perinatal/Infantile-Onset HPP

Long-term data were collected in 68 STRENSIQ-treated patients with perinatal/infantile onset HPP in Studies 1 and 2 and an additional 10 patients enrolled in Study 2. The longest duration of follow-up in the 78 patients was 7 years (84 months). At point of last contact, 69/78 (88%) STRENSIQ-treated patients had survived.

14.2 Juvenile-Onset HPP

Study 3 was a prospective open-label 24-week trial that included 8 juvenile-onset HPP patients and 5 perinatal/ infantile-onset HPP patients; 11/13 (85%) were male and 12/13 (92%) were white *[see Clinical Studies (14.1)]*. On study entry, patients were 6 to 12 years of age. All 8 juvenile-onset patients entered the extension study and were treated for at least 48 months. At trial entry, patients were randomized to receive subcutaneous STRENSIQ 6 mg/kg per week or 9 mg/kg per week. Two patients received dose reductions during the primary treatment period, including one patient who experienced a decrease in vitamin B6 levels and one patient who experienced recurrent injection site reactions. During the extension phase, the dosing regimen for all patients was initially changed to 3 mg/kg per week. Dosing was subsequently increased to 6 mg/kg per week, with no patients requiring doses higher than 6 mg/kg per week. The recommended dosage regimen of STRENSIQ for the treatment of juvenile-onset HPP is 6 mg/kg per week *[see Dosage and Administration (2.1)]*.

Growth in Juvenile-Onset HPP

Height and weight measurements (as measured by Z-scores) in 8 STRENSIQ-treated juvenile-onset HPP patients were compared with a historical cohort of 32 untreated patients with similar clinical characteristics (Table 9). Height and weight data for historical patients were collected from medical records.

Table 9: Juvenile-Onset Height and Weight Measurements as Measured by Z-Score (Study 3)

	Height Z-score				Weight Z-score			
	Baseline		Last Assessment		Baseline		Last Assessment	
	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max	Mean	Min, Max
STRENSIQ (N=8)*	-1.5	-3.8, 0	-0.9	-2, 0	-1.1	-3.5, 2.3	0	-1.3, 2.2
Control (N=32)**	-1.1	-4.9, 2.6	-1.1	-4.9, 1.8	-1.2	-5, 2.1	-1	-5.7, 2.1

* The mean time interval between baseline and last assessment was 55 months (range was 53 months to 60 months).
** The mean time interval between baseline and last assessment was 61 months (range was 19 months to 109 months).

Skeletal Manifestations in Juvenile-Onset HPP

Radiographs from 8 STRENSIQ-treated juvenile-onset HPP patients and 32 historical controls were compared to assess HPP-related rickets using the 7-point RGI-C (Radiographic Global Impression of Change) scale. Patients who achieved a RGI-C score of 2 or higher (corresponding to substantial healing of rickets) were classified as being responders to treatment. All 8 treated patients were rated as responders by Month 54 of treatment. The mean duration between the baseline and last RGI-C assessments for control patients was 56 months (range was 8 to 95 months). At last assessment, 2/32 (6%) of control patients were rated as responders.

Eight of 20 (40%) patients with juvenile-onset HPP experienced new fractures during the course of treatment. There were insufficient data to assess the effect of STRENSIQ on fractures.

Gait/Mobility in Juvenile-Onset HPP

Gait was assessed using a modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale in 8 STRENSIQ-treated juvenile-onset HPP patients at 6-month intervals out to 36 months. Mobility was also assessed using the 6 Minute Walk Test (6MWT) in 7 of the 8 patients. Step length improved by at least 1 point in either foot in 6/8 patients compared to 1/6 (17%) control patients. The proportion of patients who had 6MWT percent predicted values within the normal range for age, sex, and height-matched peers increased from 0/8 patients at baseline to 6/6 patients (100%) by Month 48 and all 6 were also able to walk longer distances at this time point compared to baseline.

Long-Term Extension Trials in Juvenile-Onset HPP

Long-term data were collected in 8 patients with juvenile-onset HPP treated with STRENSIQ for at least 6 years (72 months). At last assessment, 7 patients with available 6MWT results had maintained improvements in gait/mobility.

16 HOW SUPPLIED/STORAGE AND HANDLING

STRENSIQ is supplied as a sterile, nonpyrogenic, preservative-free, clear, slightly opalescent or opalescent, colorless to slightly yellow aqueous solution; a few small translucent or white particles may be present. The product is available as single-dose vials in a carton of one (1) or twelve (12) vials at the following strengths:

Table 10: STRENSIQ Vial Presentations

Strength	National Drug Code (NDC)	Quantity of Vials in Carton
18 mg/0.45 mL	NDC 25682-010-01	1
	NDC 25682-010-12	12
28 mg/0.7 mL	NDC 25682-013-01	1
	NDC 25682-013-12	12
40 mg/mL	NDC-25682-016-01	1
	NDC-25682-016-12	12
For pediatric patients 40 kg and greater		
80 mg/0.8 mL	NDC 25682-019-01	1

Strength	National Drug Code (NDC)	Quantity of Vials in Carton
	NDC 25682-019-12	12

STRENSIQ vials must be stored in the original carton until the time of use under refrigerated conditions at 2°C to 8°C (36°F to 46°F) and protected from light.

Once removed from refrigeration, STRENSIQ should be administered within 3 hours.

Do not use beyond the expiration date stamped on the carton.

DO NOT FREEZE OR SHAKE.

Vials are for one time use only. Discard any unused product.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Advise patients or caregivers of the following:

Preparation

- When preparing a volume for injection greater than 1 mL, split the volume equally between two syringes, and administer two injections. When administering the two injections, use two separate injection sites.
- Take the unopened STRENSIQ vial(s) out of the refrigerator 15 to 30 minutes before injecting to allow the liquid to reach room temperature.
- Inspect the solution in the vial(s) for particulate matter and discoloration.
- Assemble injection supplies. Administer STRENSIQ using sterile disposable syringes and injection needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy. Always use a new syringe and needle.
- Remove vial cap, aseptically prepare the vial and insert the syringe into the vial to withdraw the prescribed dose for administration.
- Remove any air bubbles in the syringe and verify the correct dose.
- STRENSIQ vials are for one time use only. Discard any unused product *[see Dosage and Administration (2.3)]*.

Administration

- Administer STRENSIQ within 3 hours upon removal of the vial(s) from refrigeration.
- Rotate the injection site to reduce the risk of lipohypertrophy and injection site atrophy.
- Do NOT administer injections in areas that are reddened, inflamed, or swollen.

- Inject STRENSIQ subcutaneously into the determined site and properly dispose of the syringe and needle *[see Dosage and Administration (2.4)]*.

Hypersensitivity Reactions

- Reactions related to administration and injection may occur during and after STRENSIQ treatment. Inform patients and/or caregivers of the signs and symptoms of hypersensitivity reactions and have them seek immediate medical care should signs and symptoms occur *[see Warnings and Precautions (5.1)]*.

Lipodystrophy

- Lipohypertrophy (enlargement or thickening of tissue) and localized atrophy (depression in the skin) have been reported at injection sites after several months. Follow proper injection technique and rotate injection sites *[see Warnings and Precautions (5.2)]*.

Possible Immune-Mediated Clinical Effects

- Anti-drug antibodies may develop during treatment which may interfere with STRENSIQ's pharmacologic action. Inform patients or their caregivers to contact their healthcare provider if they experience worsening symptoms of HPP (e.g., increased respiratory support, increased difficulty walking, new fractures) *[see Warnings and Precautions (5.4)]*.

Hypophosphatasia (HPP) Registry

- A registry has been established in order to better understand HPP in the population, and to monitor and evaluate long-term treatment effects of STRENSIQ. Patients and their caregivers should be encouraged to participate and advised that their participation is voluntary and may involve long-term follow-up. For more information, visit www.hppregistry.com

STRENSIQ is manufactured by:

Alexion Pharmaceuticals, Inc.

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