PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine is to be supplied upon a physician's prescription only

Strensiq® 40 mg/ml

Solution for subcutaneous injection

The active ingredient and its concentration:
Each 1 ml contains:
asfotase alfa 40 mg

Strensiq® 100 mg/ml

Solution for subcutaneous injection

The active ingredient and its concentration:
Each 1 ml contains:
asfotase alfa 100 mg

For the list of excipients, please see section 6.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, refer to your physician or pharmacist.
This medicine has been prescribed for your illness. Do not pass it on to others. It may harm them, even if you think that their illness is similar to yours.

In addition to the leaflet, there is a patient safety information card for Strensiq. This card contains important safety information that you need to know, before commencing treatment and during the course of the treatment with Strensiq and adhere to. Read the patient safety information card and this patient leaflet before commencing use of this medicine. Keep the card for further review, if necessary

1. What is the medicine used for?

Strensiq is a medicine used to treat the inherited disease hypophosphatasia that started in childhood.
Strensiq is indicated for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease.

Therapeutic group: Other alimentary tract and metabolism products, Enzymes.

Patients with hypophosphatasia have low levels of an enzyme called alkaline phosphatase that is important for various body functions, including the proper hardening of bones and teeth. Patients have problems with bone growth and strength, which can lead to broken bones, bone pain, and difficulty walking, as well as difficulties with breathing and a risk of seizures (fits).

The active substance in Strensiq can replace the missing enzyme (alkaline phosphatase) in hypophosphatasia. It is used for long-term enzyme replacement treatment to manage symptoms Strensiq has shown benefits for patients' mineralization of the skeleton and growth.

2. Before using this medicine:

Do not use the medicine if:
• You are severly hypersensitive (allergic) to the active ingredient [(asfotase alfa), see section 2: "Special warnings regarding the use of this medicine" below] or to any of the other ingredients this medicine contains (see section 6).

Special warnings regarding the use of this medicine, talk to your doctor before using Strensiq

- Patients receiving asfotase alfa have had allergic reactions including life threatening allergic reactions requiring medical treatment similar to anaphylaxis. Patients who experienced anaphylaxis-like symptoms had difficulty breathing, choking sensation, nausea, swelling around the eyes, and dizziness. The reactions occurred within minutes after taking asfotase alfa and can occur in patients who were taking asfotase alfa for more than one year. **If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately**.
  Should you experience anaphylactic reaction, or an event with similar symptoms, your doctor will discuss with you the next steps and the possibility to restart Strensiq under medical supervision. Always follow the instructions provided by your doctor.
- The development of blood proteins against Strensiq, also called anti-drug antibodies, may occur during the treatment. Talk to your doctor if you experience decreased efficacy with Strensiq.
- Fatty lumps or decreased fatty tissue on the surface of the skin (localized lipodystrophy) have been reported at injection sites after several months in patients using Strensiq. Read section 3 carefully to know the injection recommendations. This is important to rotate the injection from among the following sites to reduce the risk of lipodystrophy: abdominal area, thigh, or deltoid.
- In studies, some eye-related side-effects (e.g. calcium build-up on the eye [conjunctival and corneal calcification]) have been reported both in patients using Strensiq and those who were not, probably associated with hypophosphatasia. **Talk to your doctor in case of problems with your vision.**
- Early fusion of the bones of the head (craniosynostosis) in children below 5 years of age has been reported in clinical studies of infants with hypophosphatasia, with and without use of Strensiq. **Talk to your doctor if you notice any change in the shape of your infant's head.**
- If you are treated with Strensiq, you may experience a reaction at the injection site (pain, nodule, rash, discoloration) during the injection of the medicine or during the hours following the injection. **If you experience any severe reaction at the injection site, tell your doctor immediately.**
- Increase of parathyroid hormone concentration and low calcium levels have been reported in studies. As a consequence, your doctor may ask you to take supplements of calcium and oral vitamin D if needed.
- Weight gain may occur during your treatment with Strensiq. Your doctor will provide dietary advice as necessary.

Other medicines and Strensiq

Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines, including non-prescription drugs and nutrition supplements.

If you need to undergo laboratory tests (giving blood for testing), tell your physician that you are treated with Strensiq. Strensiq may cause some tests to show wrongly higher or lower results. Therefore another type of test may need to be used if you are treated with Strensiq.

Tests and follow up
The physician may perform periodic follow up of early fusion of the bones of the head and intracranial pressure in children below 5 years of age.
In addition, the physician may perform periodic examinations of the eyes and ultrasound of the kidneys and may monitor calcium and parathyroid hormone levels in the blood.

Pregnancy
Strensiq should not be used during pregnancy. The use of effective birth control during treatment should be considered in women who are able to get pregnant.

Breast-feeding
It is not known whether Strensiq can pass into breast milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Strensiq, considering the benefit of breast-feeding to the baby and the benefit of Strensiq to the mother.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
This medicine is not expected to have any effect on the ability to drive or use machines.

Important information about some of the ingredients of this medicine
This medicine contains less than 1 mmol sodium (23 mg) per vial, which means it is essentially 'sodium-free'.

3. How to use this medicine

- Always use this medicine exactly as described in this leaflet or as your doctor, or pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure about the dosage or method of administration.
- Treatment should be initiated by a physician experienced in the management of patients with metabolic or bone related diseases. How to use Strensiq will be explained to you by the doctor. After being trained by the doctor or specialized nurse, you can inject Strensiq yourself at home.
- The medicine is given by subcutaneous injection only.
- Efficacy and safety data in patients with hypophosphatasia over 18 years old is limited.
- **Do not exceed the recommended dose.**

The dosage and administration will be determined by the physician only, based on body weight. The usual recommended dosage is:

- The correct dose will be calculated by your doctor and consists of a total of 6 mg of asfotase alfa per kg of body weight every week, given either as an injection of 1 mg/kg asfotase alfa 6 times per week or as 2 mg/kg asfotase alfa 3 times per week depending on the recommendation of your doctor. Each dose will be administered by injection under the skin (subcutaneous). (See the dosing chart below for detailed information on the volume to be injected, and the type of vials to be used, based on your weight).

- Doses will need to be adjusted regularly by your doctor as the body weight changes.
- The maximum volume per injection should not exceed 1 ml. If more than 1 ml is required, you need to do multiple injections immediately one after the other.

If injecting 3 times per week

Body Weight (kg)	Volume to be injected	Color of the vial's cap to be used
3	0.15 ml	Dark blue/Orange
4	0.20 ml	Dark blue/Orange
5	0.25 ml	Dark blue/Orange
6	0.30 ml	Dark blue/Orange
7	0.35 ml	Orange
8	0.40 ml	Orange
9	0.45 ml	Orange
10	0.50 ml	Light blue
11	0.55 ml	Light blue
12	0.60 ml	Light blue
13	0.65 ml	Light blue
14	0.70 ml	Light blue
15	0.75 ml	Pink
16	0.80 ml	Pink
17	0.85 ml	Pink
18	0.90 ml	Pink
19	0.95 ml	Pink
20	1 ml	Pink
25	0.50 ml	Green
30	0.60 ml	Green
35	0.70 ml	Green
40	0.80 ml	Green

If injecting 6 times per week

Body Weight (kg)	Volume to be injected	Color of the vial's cap to be used
6	0.15 ml	Dark blue/Orange
7	0.18 ml	Dark blue/Orange
8	0.20 ml	Dark blue/Orange
9	0.23 ml	Dark blue/Orange
10	0.25 ml	Dark blue/Orange
11	0.28 ml	Dark blue/Orange
12	0.30 ml	Dark blue/Orange
13	0.33 ml	Orange
14	0.35 ml	Orange
15	0.38 ml	Orange
16	0.40 ml	Orange
17	0.43 ml	Orange
18	0.45 ml	Orange
19	0.48 ml	Light blue
20	0.50 ml	Light blue
25	0.63 ml	Light blue
30	0.75 ml	Pink
35	0.88 ml	Pink
40	1 ml	Pink
50	0.50 ml	Green
60	0.60 ml	Green
70	0.70 ml	Green
80	0.80 ml	Green
90	0.90 ml	Green (x2)
100	1 ml	Green (x2)

Injection recommendations

- You may experience a reaction at the injection site. Read section 4 carefully: “Side effects”, to know what side effects can occur before using this medicine.
- When injecting regularly, the injection site should be changed between different areas of the body to help reduce potential pain and irritation,
- Areas with a good amount of fat below the skin (thighs, arms (deltoids), abdomen, and buttocks) are the most suitable areas to inject. Please discuss with you doctor or nurse the best sites for you.

Before injecting Strensiq, please read the following instructions carefully:

- Each vial is for **single use** and should only be punctured once. Strensiq liquid should look clear, slightly opalescent or opalescent, colourless to slightly yellow and may have a few small translucent or. white particles in it. Do not use it if the liquid is discoloured or contains any lumps or large particles in it and get a new vial. Any unused medicinal product or waste material should be disposed of in accordance with local requirements
- If you are injecting this medicine yourself, you will be shown how to prepare and inject the medicine by your doctor, pharmacist or nurse. Do not inject this medicine yourself unless you have received training and you understand the procedure.

How to inject the medicine

Step 1: Preparing the Strensiq dose

1. Wash your hands thoroughly with soap and water.
2. 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). Upon Removal of the vial(s) from refrigeration, Strensiq should be used within 3 hours maximum (see section 5. How to store Strensiq).
3. Remove the protective cap from the Strensiq vial(s). Remove the protective plastic from the syringe to be used.
4. Always use a new syringe contained in a protective plastic.
5. Place a larger bore needle (e.g. 25G) on the empty syringe and with the protective cap on,
   push down and turn clockwise the needle onto the syringe until it is tight.
6. Remove the plastic cap covering the syringe needle. Pay attention not to hurt yourself with the
   needle.
7. Pull the plunger back to draw air into the syringe equal to your dose.

Step 2: Withdrawing Strensiq solution from the vial

1. Holding the syringe and vial, insert the needle through the sterile rubber seal and into the vial.

2. push the plunger in completely to inject air into the vial.

3. Invert the vial and syringe. With the needle in the solution, pull the plunger to withdraw the correct dose into the syringe.

4. Before removing the needle from the vial, check that the appropriate volume has been withdrawn and check the syringe for air bubbles. In the event that bubbles appear in the syringe, hold the syringe with the needle pointing upwards and gently tap the side of the syringe until the bubbles rise to the top.

5. Once all the bubbles are at the top of the syringe, gently push on the plunger to force the bubbles out of the syringe and back into the vial.

6. After removing the bubbles, recheck the dose of medication in the syringe to be sure you have drawn up the correct amount. You may need to use several vials to withdraw the complete amount needed to reach the correct dose.

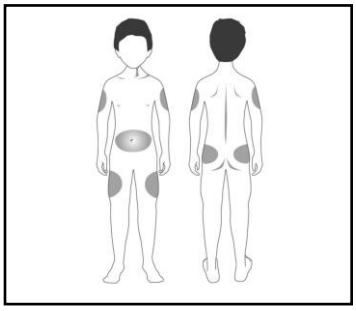
<u>Step 3: Placing the needle for injection on the syringe</u>

1. Remove the needle from the vial. Recap with one hand by placing the cap on a flat surface, slide the needle into the cap, lift it up and snap it on securely using only one hand.
2. Carefully remove the larger bore needle pushing down and turning counterclockwise. Dispose the needle with the protective cap in your sharps container
3. Place a smaller bore needle (e.g. 27 or 29G) on the filled syringe and with the protective cap on, push down and turn clockwise the needle onto the syringe until it is tight. Pull the cap straight off the needle.
4. Hold the syringe with the needle pointing up and tap the barrel of the syringe with your finger to remove any air bubbles.

Control visually that the volume contained into the syringe is correct.
The volume per injection should not exceed 1 ml. If it is the case, multiple injections should be done at different sites.
You are now ready to inject the correct dose.

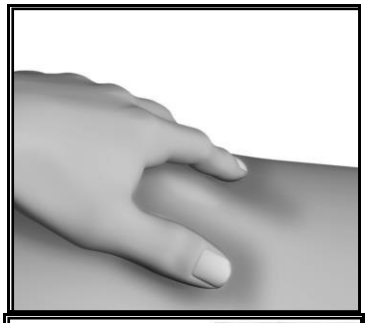
Step 4: Injecting Strensiq

1. Choose an injection site (thighs, abdomen, arms (deltoids) buttocks). Most suitable areas for injection are marked grey in the picture. Your doctor will advise you on the possible injection sites.



NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor about anything you find.

2. Gently pinch the skin of the chosen injection area between your thumb and index finger.

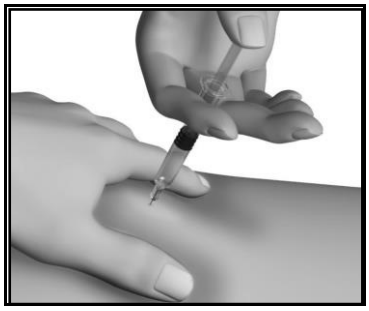


3. Holding the syringe like a pencil or a dart, insert the needle into the raised skin so it is at an angle of between 45º and 90º to the skin surface.

   For patients who have little fat under the skin or thin skin, a 45º angle may be preferable.

4. While continuing to hold the skin, push the syringe plunger to inject the medicine slowly, and steadily all the way in.

5. Remove the needle, release the skin fold and gently place a piece of cotton wool or gauze over the injection site for a few seconds.



This will help seal the punctured tissue and prevent any leakage. Do not rub the injection site after injection.

If you need a second injection for your prescribed dose, get another Strensiq vial and repeat steps 1 through 4.

Step 5: Disposing of supplies

Please collect your syringes, vials and needle in a sharps container. Your doctor, pharmacist or nurse will advise you on how you can obtain a sharps container.

If you have accidentally injected an overdose or if a child has accidentally swallowed the medicine, refer immediately to a physician or a hospital emergency room and bring the package of the medicine with you.

If you forgot to inject this medicine at the scheduled time, do not inject a double dose to make up for a forgotten dose and contact your physician for advice.

Always continue with the treatment as recommended by your physician.
Even if there is an improvement in your health condition, do not stop taking this medicine without consulting your physician.

Do not take medicines in the dark! Check the label and the dose each time you take your medicine. Wear glasses if you need them.

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

4. Side effects

Like all medicines, Strensiq can cause side effects,.in some of the users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them.

The most serious side effects seen in patients receiving asfotase alfa have been allergic reactions including life threatening allergic reactions requiring medical treatment similar to anaphylaxis. This side effect is common [may affect up to 1 in 10 people]). Patients who experienced these serious allergic reactions had difficulty breathing, choking sensation, nausea, swelling around the eyes, and dizziness. The reactions occurred within minutes after using asfotase alfa and can occur in patients who were using asfotase alfa for more than one year**. If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately.**

Additionally, other allergic reactions (hypersensitivity) which may appear as redness (erythema), fever (pyrexia), rash, itchiness (pruritis), irritability, feeling sick (nausea), throwing up (vomiting), pain, chills (rigor), numbness of the mouth (hypoaesthesia oral), headache, blushing (flushing), fast beating of the heart (tachycardia), and cough may occur commonly**. If you experience any of these symptoms, discontinue Strensiq and seek medical help immediately.**

Very common side effects: may affect more than 1 in 10 patients

- Reactions at the injection site during the injection of the medicine or during the hours following the injection (which can lead to redness, discolorations, itching, pain fatty lumps or decreased fatty tissue on the surface of the skin, skin hypopigmentation, and/or swelling).
- Fever (pyrexia),
- Irritability
- Skin redness (erythema)
- Pain in hands and feet (pain in extremity)
- Bruise (contusion)
- Headache

Common side effects: may affect up to 1 in 10 patients

- Stretched skin, skin discolouration
- Feeling sick (nausea)
- Numbness of the mouth (hypoaesthesia oral)
- Aching muscles (myalgia)
- Scar
- Increased tendency to bruise
- Hot flush
- Infection of skin at injection site (injection site cellulitis)
- Reduced levels of calcium in the blood (hypocalcaemia)
- Kidney stones (nephrolithiasis)

If any of the side effects appears, if any of the side effects worsens, or if you experience any possible side effects not mentioned in this leaflet, consult your physician.

Reporting of side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il) which links to an online form for reporting side effects, or by the following link: https://sideeffects.health.gov.il/
and by emailing the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

5. How to store the medicine

- Avoid poisoning! This medicine and any other medicine must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by your physician.
- Do not use the medicine after the expiry date (exp. date) which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C). Do not freeze. Store in the original package in order to protect from light.
- After opening the vial, the product should be used immediately (within 3 hours maximum at room temperature, between 23°C and 27°C) .
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:
Sodium chloride, Sodium phosphate dibasic heptahydrate, Sodium phosphate monobasic monohydrate, Water for injections.

What does the medicine look like and what is the content of the package
Strensiq is presented as a clear, slightly opalescent or opalescent, colourless to slightly yellow aqueous solution for injection. A few small translucent or white particles may be present

Strensiq 40 mg/ml is contained in vials of 0.3 ml, 0.45 ml, 0.7 ml or 1 ml of solution.

- Each vial of 0.3 ml solution has a dark blue cap and contains 12 mg of asfotase alfa.
- Each vial of 0.45 ml solution has an orange cap and contains 18 mg of asfotase alfa.

- Each vial of 0.7 ml solution has a light blue cap and contains 28 mg of asfotase alfa.
- Each vial of 1 ml solution has a pink cap and contains 40 mg of asfotase alfa.

Strensiq 100 mg/ml is contained in vials of 0.8 ml of solution.

- Each vial of 0.8 ml solution has a green cap and contains 80 mg of asfotase alfa.

Pack sizes: 1 vial or 12 vials.
Not all pack sizes may be marketed.

Manufacturer's name and address:
Alexion Pharma International Operations Limited, Dublin, Ireland.

Registration holder's name and address:
Alexion Pharma Israel Ltd, P.O.Box 7063, Petach Tikva 4917001.

Drugs registration numbers at the national medicines registry of the Ministry of Health:
Strensiq® 40 mg/ml: 155-43-34542
Strensiq® 100 mg/ml: 155-44-34545

Revised in December 2023 according to MOHs guidelines

Strensiq sol for inf PIL vr 01B