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Summary of the risk management plan (RMP) for Strensiq (asfotase alfa)

This is a summary of the risk management plan (RMP) for Strensiq, which details the measures to be taken in order to ensure that Strensiq is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Strensiq, which can be found on Strensiq's EPAR page.

Overview of disease epidemiology

Strensiq is a medicine used to treat hypophosphatasia (HPP), a rare genetic disease of the bones. It can affect men and women of any age, from infancy through adulthood. Strensiq is used in HPP that started in childhood. The incidence (number of newly diagnosed cases) of severe forms is estimated at 1 per 100,000 live births. People with HPP have low levels of an enzyme called alkaline phosphatase that is necessary for normal bone development and the hardening of the bones. Patients with both childhood- and adult-onset HPP have complications which may include deformity of bones, abnormal growth and decreased muscle performance. These can rapidly lead to progressive damage to multiple vital organs, for example lungs, bone muscle, brain and kidney, leading to respiratory failure, fractures, weakness, developmental delays, seizures and kidney stones.

Summary of treatment benefits

Strensiq contains the active substance asfotase alfa and is available as a solution for injection under the skin.

Strensiq has been studied in one main study in 13 children between 6 and 12 years of age. Patients were given either 2 mg/kg or 3 mg/kg Strensiq three times a week for 24 weeks. The main measure to indicate effectiveness of the medicine was the improvement in x-ray appearance of the wrists and knee joints of patients before and after treatment with Strensiq. X-rays of children given Strensiq were also compared with similar x-rays available from 16 children who had not received Strensiq ('historical controls'). The study also looked at other measures of effectiveness such as growth in height. This study showed that children given Strensiq had an improvement in their joint structure as demonstrated by x-rays and most of them seemed to gain in height. In the historical controls, most children did not experience similar improvements in their joints or gain in height over a comparable period of time.

The effectiveness of Strensiq was also generally supported by several additional small studies. Some of the studies also looked at the dose of 1 mg/kg Strensiq given six times a week.

Unknowns relating to treatment benefits

Strensiq has not been studied in the following groups of patients:

- patients over 65 years of age;

- non-Caucasian (non-white) patients;
- pregnant women;
- patients with severe liver or kidney disorders;
- patients who use the medicine long-term.

The effect of Strensiq on other HPP disease characteristics like seizure, craniosynostosis (early fusion of the bones of the head in children below 5 years of age) and ectopic calcification (calcium deposit in inner membrane of the eyelid and kidney) is not known.

There is limited information on the treatment benefit in patients above 13 years of age.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Reactions at the site of injection (injection site reactions)	In clinical studies of Strensiq at least 1 out of 2 patients experienced reactions at the site of the injection. The most common reactions are: rash, redness, discolouration and thinning of the skin, inflammation, bumps, hives, pain and itching of the injection site Not all patients experienced all reactions: These reactions were usually mild in nature and resolved over time.	Reactions at the injection site can be prevented by injecting the medicine correctly, in line with the instructions of the product information. Rotating the site of these injections will also help reduce reactions at a particular injection site.
Development of antibodies against the medicine (immunogenicity)	Because Strensiq contains a protein, it could potentially be detected as 'foreign' by the immune system, which could then produce antibodies against Strensiq. Antibodies to the medicine have been observed in patients in the clinical studies. These antibodies could potentially cause side effects such as allergic reactions. Symptoms of such reactions include low blood pressure, vomiting, difficulty breathing, fast heart rate, hives or rash. In the clinical studies with Strensiq, patients who developed antibodies against Strensiq did not show signs of allergic reactions. In addition, antibodies against the	Patients who experience any symptom of an allergic reaction, should inform their doctor immediately. If symptoms of a severe allergic reaction occur, Strensiq should be discontinued immediately and appropriate medical treatment initiated.

Risk	What is known	Preventability
	medicine could potentially reduce the effect of the medicine.	
Reactions associated with the injection, but which do not occur at the injection site (injection associated reactions)	Reactions associated with the injection, such as shaking, chills, headache, fever, nausea and numbness of the lips have been experienced by patients in the clinical studies.	These reactions are not preventable. Patients who experience such reactions should tell their doctor immediately. The patients may need to be given additional medicines (antihistamines or corticosteroids) along with the injection of Strensiq to treat these reactions.

Important potential risks

Risk	What is known
Calcium deposit in inner membrane of the eyelid, surface of the eye and kidney (ectopic calcification)	Cases of deposits of calcium salts in the kidney, on the inner membrane of the eyelid and surface of the eye have been reported during clinical studies with Strensiq, but it is not known if those events are associated with Strensiq or with the patients' disease.
Early fusion of the bones of the head in children below 5 years of age (craniosynostosis)	Cases of early fusion of the bones of the head have been reported during clinical studies with Strensiq in young children (below 5 years of age), but it is not known if those events are associated with Strensiq or with the patients' disease.
Improper use of medication (medication errors)	There are a few cases where the incorrect dose was administered to a patient during clinical studies. No side effects were reported in these patients. The medicine's carton and label will therefore be colour-coded to better distinguish between presentations. In addition, booklets and animated injection guides with detailed information on the correct use and administration of the medicine will be available to patients and carers.

Missing information

Risk	What is known
Limited information on use in patients with kidney and liver impairment	Strensiq has not been specifically studied in patients with liver and kidney impairment.
Limited information on Strensiq's use in	Experience on the use of Strensiq during pregnancy in humans is limited.

Risk	What is known
pregnant and breastfeeding women	Strensiq is not recommended during pregnancy and in women who can have children and who are not using contraception. Breastfeeding should be discontinued during treatment with Strensiq. Women who are pregnant or breastfeeding, think they may be pregnant or are planning to have a baby, should ask their doctor or pharmacist for advice before taking this medicine.
Limited information on use in older patients	Strensiq has not been specifically studied in older patients.
Long-term safety and effectiveness	The experience regarding long term use of Strensiq in HPP patients is limited.
Limited information in non-Caucasian patients	The experience regarding the long term use of Strensiq in non-Caucasian patients is limited.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Strensiq can be found on Strensiq's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Strensiq's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Injection site reactions; Medication errors

Risk minimisation measure: Educational material
Objective and rationale: To provide advice on the management of injection site reactions; to reduce the risk of medication errors.
Description: Educational material will be provided to patients and caregivers by the physician. These will include separate Injection Guides for Patients who self-inject and for parents/caregivers who inject infant patients. An animated Injection Guide will also be made available. The guides include information such as how to choose the injection site; how to inject using aseptic techniques; how to carry out and record the injection; how to maintain the cold chain during storage and travel; how to administer the correct dose and how to report side effects

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
ALX-HPP-501: An observational, longitudinal, prospective, long-term registry of patients with hypophosphatasia	To collect and evaluate data on safety and effectiveness of the use of Strensiq in HPP patients.	Effectiveness data on the use of Strensiq in HPP patients.	Planned	Interim data analysis yearly
Efficacy data from patients 13-18 years of age enrolled in ongoing clinical studies (ENB-008-10 and ENB-009-10)	RGI-C scores, height, weight change, and biomarker measurement in patients 13 to 18 years of age.	Limited efficacy data in patient aged 13 to 18 years of age.	Planned	Final report to be submitted 18 months after EC decision (February 2017)
Study in patents >18 years of age	Pharmacokinetic data on plasma levels of Strensiq following administration of the dose proven to be effective in children (6.0 mg/kg/week). Dose response data on the biomarkers inorganic pyrophosphate (PPi) and pyridoxal-5′-phosphate (PLP) in approximately 27 patients.	Limited efficacy data in patients above 18 years of age.	Planned	Final report to be submitted 18 months after EC decision (February 2017)

Studies which are a condition of the marketing authorisation

The company has the obligation to carry out all the three studies listed in the table above.

Summary of changes to the risk management plan over time

This summary was last updated in 07-2015.