Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for somatropin / Saizen

This is a summary of the Risk Management Plan (RMP) for Saizen. The RMP details important risks of Saizen and how these risks can be minimised, and how more information will be obtained about Saizen's risks and uncertainties (missing information).

Saizen's Summary of Product Characteristics (SmPC) and its Product Leaflet (PL) give essential information to healthcare professionals and patients on how Saizen should be used.

Important new concerns or changes to the current ones will be included in updates of Saizen's RMP.

I. The Medicine and What it is used for

Saizen is authorised for indications:

Children and adolescents:

- Growth failure in children caused by decreased or absent secretion of endogenous growth hormone (GH).
- Growth failure in girls with gonadal dysgenesis (Turner syndrome [TS]), confirmed by chromosomal analysis.
- Growth failure in prepubertal children due to chronic renal failure (CRF).
- Growth disturbance (current height Standard Deviation Score [SDS] <-2.5 and parental adjusted height SDS <-1) in short children born small for gestational age (SGA) with a birth weight and/or length below -2 Standard Deviation (SD), who failed to show catch-up growth (Height Velocity SDS <0 during the last year) by 4 years of age or later.

Adults:

- Replacement therapy in adults with pronounced growth hormone deficiency (GHD) as diagnosed by a single dynamic test for GHD. Patients must also fulfil the following criteria:

Childhood onset:

- Patients who were diagnosed as GH deficient during childhood, must be retested and their GHD confirmed before replacement therapy with Saizen is started.

Adult onset:

- Patients must have GHD as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using GH may begin.

It contains somatropin / Saizen as the active substance and it is given by subcutaneous (SC) (Saizen powder and solvent for solution for injection and Saizen solution for injection) and intramuscular (IM) injection (Saizen powder and solvent for solution for injection).

It is available in the following pharmaceutical forms and strengths:

- Saizen powder and solvent for solution for injection 8 mg for SC and IM administration, and 8 mg Click.easy for SC administration.
- Saizen solution for injection 5.83 mg/mL (6 mg somatropin) and 8 mg/mL (12 mg and 20 mg somatropin) for SC administration.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Saizen, together with measures to minimise such risks and the proposed studies for learning more about Saizen risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine Risk Minimisation Measures.

II.A List of Important Risks and Missing Information

Important risks of Saizen are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Saizen. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Insulin resistance with hyperinsulinism, hyperglycemia • Idiopathic intracranial hypertension

Important potential risks	• Neoplasm
	  • New neoplasm
	  • Neoplasm recurrences/progression
	  • Second neoplasm

List of Important Risks and Missing Information	
	• Intracranial hemorrhage and intracranial aneurysm • Immunogenicity
Missing information	• Use in patients with cardiac disease • Long-term safety in subjects born SGA

II.B Summary of Important Risks

Important identified risk: Insulin resistance with hyperinsulinism, hyperglycemia	
Evidence for linking the risk to the medicine	Insulin resistance can lead to hyperglycemia. Persistent hyperglycemia over many years can affect the kidney (renal insufficiency), eyes (impairment of retina), nerves (polyneuropathy, stroke), heart (e.g., myocardial infarction) and wound healing (impaired healing which may be complicated by infections or result in amputations, e.g., diabetic foot syndrome). These complications usually manifest in advanced adult age and not during treatment in childhood. The elevated blood glucose levels have to be treated with diet, oral antidiabetic drugs and/or insulin. The treating physician may consider a discontinuation of somatropin / Saizen. After discontinuation of somatropin, hyperglycemia commonly resolves. The development of complications depends on the severity of the elevated blood sugar level and on the adequate and consequent treatment of hyperglycemia. However, complications cannot always be prevented even if the blood sugar level is corrected. Also, acute condition which may potentially occur with hyperglycemia and include diabetic ketoacidosis or diabetic coma. However, such cases were very rarely reported and did not occur with somatropin / Saizen but with another somatropin containing product (Serostim) which was used for HIV wasting syndrome. The HIV-patients had other concurrent medical conditions which led to diabetic acidosis or diabetic coma, and it is not likely that the event was caused by Serostim. The well-being of the patient might be impacted by the previously described potential complications and procedures. Insulin resistance with hyperinsulinism and hyperglycemia were reported in Company-sponsored studies and well-documented spontaneous case reports. However, if the patients are monitored regularly by the treating physician and if symptoms of insulin resistance, hyperinsulinism or, hyperglycemia are detected early, the event can be treated, or the decision can be taken to discontinue somatropin.
Risk factors and risk groups	Saizen should be used with caution in patients with diabetes mellitus (adjustment of their antidiabetic therapy may be required) or with a family history of diabetes mellitus, especially those who are obese or older. Some subgroups of patients such as patients born SGA, TS, adult growth hormone deficiency syndrome (AGHD) and Prader-Willi syndrome have a risk of developing hyperglycemia, hyperinsulinism and insulin resistance (Sas et al., 2000; Sas et al., 2001; Giavoli et al., 2004; Christopher et al., 1998). Therefore, particularly these certain subgroups should carefully be monitored during GH therapy.
Risk Minimisation Measures	**Routine Risk Minimisation Measures**: European Union Summary of Product Characteristics (EU SmPC) section 4.4 EU SmPC section 4.8 Package Leaflet (PL) section 2 PL section 4 Prescription only medicine

Important identified risk: Insulin resistance with hyperinsulinism, hyperglycemia	
	Additional Risk Minimisation Measures None
Additional Pharmacovigilance Activities	**Additional Pharmacovigilance Activities:** SALTO [EMR 200098-008] Prospective, single-cohort, multicenter observational long-term study in short children born SGA after treatment with Saizen. See section II.C below of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Idiopathic Intracranial Hypertension	
Evidence for linking the risk to the medicine	If the elevated increased cerebrospinal fluid pressure remains untreated, permanent visual loss or blindness may result (Binder et al., 2004; Acheson, 2006). Idiopathic intracranial hypertension was reported in Company-sponsored studies and well-documented spontaneous case reports and the well-being of the patient might be impacted by the previously described potential complication. However, if symptoms of intracranial hypertension such as recurrent or persistent headache, visual impairment, nausea and/or vomiting are detected early and somatropin is discontinued, idiopathic intracranial hypertension usually recovers without sequelae.
Risk factors and risk groups	Idiopathic intracranial hypertension is more common in female patients, and in adults it is associated with obesity and has a peak incidence in 20 to 44-year-old obese women (Durcan et al., 1988). It has been related with intake of several medications such as thyroid hormones, corticosteroids, and tetracyclines (Lessell 1992; Malozowski et al., 1995; Huseman, 1984; Vyas et al., 1981). Further risk factors include endocrine disorders (Addison's disease, hypoparathyroidism, steroid withdrawal), CRF, and malnutrition (Chang et al., 1992; Guy et al., 1987; Lessell, 1992; Malozowski et al., 1995; Clayton and Cowell 2000; Watkins 1996a; Chen et al., 2014). In consequence, this means that children receiving GH for growth failure in prepubertal children due to CRF are more likely to develop idiopathic intracranial hypertension (Clayton and Cowell, 2000).
Risk minimisation measures	**Routine risk minimisation measures:** EU SmPC section 4.4 EU SmPC section 4.8 PL section 2 PL section 4 Prescription only medicine **Additional Risk Minimisation Measures** None
Additional Pharmacovigilance Activities	**Additional Pharmacovigilance Activities:** None

Important Potential Risk: Neoplasm: New Neoplasm, Neoplasm Recurrences/Progression, Second Neoplasm	
Evidence for linking the risk to the medicine	Neoplasms have to be differentiated in benign and malignant neoplasms. Malignant neoplasms finally result in a life-threatening or fatal outcome if

Important Potential Risk: Neoplasm: New Neoplasm, Neoplasm Recurrences/Progression, Second Neoplasm	
	metastases are present and vitally important organs (e.g., lung, liver, brain) are affected. Also, the location of a benign or malignant tumor can significantly impair health and may also result in fatal outcome if a vitally important organ (e.g., brain, heart) is damaged by tumor growth. Tumors in bones can lead to fractures, brain tumors can cause paralysis or disturbances of sensory and motoric nerves. Therapeutic interventions depend on the kind of tumor and its location. They may comprise irradiation, chemotherapy, surgery and use of other corrective medications. Neoplasm was reported in Company-sponsored studies and well-documented spontaneous case reports. Somatropin / Saizen contains r-hGH which mimics the naturally occurring human produced somatropin and its effector hormone is Insulin Growth Factor -1 (IGF-1). Theoretical and clinical evidence from various sources has suggested a possible link between GH (somatropin) and the development of malignant diseases. In vitro studies have shown important mitotic (cell replication) and anti-apoptotic properties (prevention of cell death) of IGF-1 that suggest a possible important role of IGF-1 in carcinogenesis. However, a significant subgroup of patients with GHD is predisposed for tumor recurrence and onset of a second neoplasm, independent of treatment with somatropin / Saizen or not. Causes for GHD are commonly intracranial tumors or their treatment which affect the pituitary gland. Tumor treatment such as irradiation and chemotherapy further predispose to development of a second neoplasm. In addition, patients with medical history of a malignant neoplasm are at a higher risk of recurrence of the malignant neoplasm. At present, there is no clinically proven evidence that somatropin induces tumors or increases the recurrence rate in patients with a medical history of tumors. In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms.
Risk factors and risk groups	GHD is an endocrinopathy which occurs commonly in cancer survivors who had either tumors affecting the hypothalamic-pituitary axis or had received cancer therapies, particularly cranial irradiation (Alvarez et al., 2007; Woodmannsee et al., 2013; Schmiegelow et al., 2000; Sklar et al., 2002). These neoplasias include benign and malignant brain tumors such as pituitary adenomas, craniopharyngeomas, meningiomas, germ cell tumors, medulloblastomas, astrocytomas, gliomas, etc. which are commonly resected and subsequently treated with cranial irradiation and/or chemotherapy (Kryzanowska-Mittermayer et al., 2015; Webb et al., 2009). But also, patients with blood cancers such as e.g., leukemia receive cranial irradiation therapy. GHD has been found in 58% of long-term survivors of childhood cancer who had received whole brain irradiation with $\geq$ 24 Gy (Gurney et al., 2006; Woodmansee et al., 2013). Pediatric patients with prior neoplasm are at an increased risk of developing second neoplasm or a neoplasm recurrence when treated with GH particularly if they had received prior radiotherapy or chemotherapy (Bell et al., 2010). Further risk factors included HIV infection, congenital diseases, or genetic predispositions, (e.g., chromosomal break syndrome, neurofibromatosis, etc.).
Risk Minimisation Measures	**Routine Risk Minimisation Measures**: EU SmPC section 4.3 EU SmPC section 4.4 EU SmPC section 4.8 (leukemia, only) PL section 2

Important Potential Risk: Neoplasm: New Neoplasm, Neoplasm Recurrences/Progression, Second Neoplasm	
	PL section 4 (leukemia, only) Prescription only medicine **Additional Risk Minimisation Measures** None
Additional Pharmacovigilance Activities	**Additional Pharmacovigilance Activities**: SALTO [EMR 200098-008] Prospective, single-cohort, multicenter observational long-term study in short children born SGA after treatment with Saizen. See section II.C below of this summary for an overview of the post-authorisation development plan. Specific adverse reaction follow-up questionnaires for safety concern: A specific ADR follow-up form 'Cancer_malignant tumors_v1.0' Other forms of routine pharmacovigilance activities for safety concern: Close monitoring of 'Second neoplasm, recurrent neoplasm'.

Important Potential Risk: Intracranial Hemorrhage and Intracranial Aneurysm	
Evidence for linking the risk to the medicine	Ischemic stroke (interruption of the blood supply in a brain artery) and cerebral bleeding (hemorrhagic stroke) can cause severe neurological deficits, depending on the severity and extent of the stroke or cerebral bleeding. Minor strokes and bleeding can resolve with no or minor deficits. A severe stroke or cerebral bleeding can result in paralysis and/or movement disorders of extremities, visual impairment, dysphagia, speech disorders and can be fatal. The therapy depends on the cause: an ischemic stroke requires either the mechanical removal of the blot clot or the medicamentous lysis of the blood clot. Alternatively, the blood clot or vascular plaque can surgically be removed, or the narrowed vessel can be dilated with a ballon or stent. A hemorrhagic stroke/cerebral bleeding may also require surgical intervention to repair the blood vessel or to remove blood to reduce the pressure on the brain. Ischemic and hemorrhagic stroke was reported in Company-sponsored studies and well-documented spontaneous case reports. However, the underlying conditions of the patient population treated with Saizen (somatropin) have to be taken into consideration. The majority of the patients had a medical history of brain tumor with radiation therapy; a medical history of brain tumor or cranial irradiation are risk factors for stroke. Other patients had risk factors such as congenital brain disorders predisposing for stroke, vascular disorders or malformations, metabolic defects predisposing for stroke and cerebral inflammatory disorders. Also, patients born SGA and with a certain genetic disorder are at higher risk (Jancevska et al., 2012). The frequency of ischemic and hemorrhagic stroke is considered higher in GH deficient patients irrespective of whether they have been treated with somatropin substitution therapy or not. A direct association between somatropin and stroke (ischemic, hemorrhagic) could not be established, so far.
Risk factors and risk groups	Patients with GHD with a medical history of brain neoplasia and/or cranial irradiation, growth failure due to other congenital diseases and patients born SGA are at a higher risk for cerebrovascular disorders. Horan et al., (2006) found a strong association between the presence of a certain GH deficient 1 (GH1) promoter haplotype and a family history of stroke at an early age. Further discussed risk factors include GH receptor polymorphism, hypertension, and inverse relationship to final adult height (Horan et al., 2006).

Important Potential Risk: Intracranial Hemorrhage and Intracranial Aneurysm	
	Patients born SGA are reported to have a higher incidence of stroke and other diseases related to vascular impairment such as e.g., metabolic syndrome, coronary artery disease (Jancevska et al., 2012). Also, the past treatment of patients with GHD may contribute to a higher risk of cerebrovascular events. Many GH deficient patients have a medical history of brain tumors (medulloblastoma, craniopharygioma, astrocytoma, etc.) which have been treated with cranial radiation therapy and chemotherapy. A medical history of brain tumor and cranial radiation therapy increases the risk of neurovascular events 100-fold compared to the general pediatric population (Campen et al., 2012). Further other congenital diseases such as Charge syndrome, brain malformation, M. Recklinghhausen (neurofibromatosis) or concomitant diseases such as cerebral vasculitis, meningitis or HIV infection are associated with a higher risk of cerebrovascular events or cardiovascular malformations (Lalani et al., 2017; Rosser et al., 2005; Kempster et al., 2016; AHA, 2017; Bodilsen et al., 2014; Benjamin et al., 2012).
Risk minimisation measures	**Routine risk minimisation measures:** Prescription only medicine **Additional Risk Minimisation Measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** A specific follow-up questionnaire is available for this important potential risk ('Stroke_v1.0')

Important Potential Risk: Immunogenicity	
Evidence for linking the risk to the medicine	Immunogenicity (development of anti-drug antibodies [ADAs]) can potentially impair the efficacy of the the product or cause adverse reactions such as local injection site reactions up to anaphylactic reactions and theoretically also autoimmune reactions (cross-reactivity of the ADA with own proteins/cells in the body). Delayed immunogenic reactions may potentially present with myalgia (muscle pain), arthralgia (joint pain) with fever, skin rash, and itching. ADAs, which may present as NAb's and anti-host-cell antibodies, were mainly reported in Company-sponsored studies. The number of well-documented spontaneous case reports was quite small. The extent of antibody development in Company-sponsored studies varied among the single studies depending on the test used for antibody determination (several different tests were used) and enrolled patient population. Many patients in the clinical studies had not been treatment-naïve prior to study enrollement, and the risk of antibody formation is higher to these patients as they had already been exposed to other recombinant exogenous somatropins. In addition, it is likely that the sensitivity and specificity among the different tests were highly variable. However, this cannot be analyzed as some tests are no longer marketed. There were no real differences of antibody formation with regard to study duration and follow-up time, which ranged between 2 to 4 years. In several cases, the antibodies were transient and became negative again during the course or end of study. Just single patients presented with a small and transient growth reduction among all patients with neutralizing antibodies (NAb's) in the Company-sponsored studies.

Important Potential Risk: Immunogenicity	
	Although no significant impact on efficacy and safety by ADAs is known, so far, the potential consequences of an immune reaction to a therapeutic protein (e.g., anaphylaxis, autoimmunity, lack of efficacy) justify the classification of 'immunogenicity' as important potential risk as these potential reactions can impair the well-being of the patient if they would occur.
Risk factors and risk groups	Antibodies can develop in all indications. In very rare instances, where short stature is due to deletion of the GH gene complex, treatment with GH may induce growth attenuating antibodies (SmPC on Saizen). Other risk factors include previous treatment with somatropin, re-exposure after a long-treatment-free interval and pre-existing antibodies from previous exposure to similar or related proteins. Patients with activated immune systems (for example those suffering from chronic infections, allergies and autoimmune/autoinflammatory diseases), may be more prone to immune responses to therapeutic proteins. In other conditions (e.g., malnutrition, advanced malignant disease, advanced HIV disease, organ failure), an immune response might be less likely to occur due to an impaired immune system. The immune response to therapeutic proteins can also be affected by the patient's age. Among the pediatric population, different levels of maturation of the immune system are seen depending on age, and discrepant immune responses to a biological product may be expected (EMEA/CHMP/BMWP/14327/2006 Rev. 1). In addition, a degraded product can have an immunogenic potential. A 4-week toxicity study in rats with an artificially aged liquid formulation showed immunogenicity after repeated administration (Saizen IB).
Risk minimisation measures	**Routine risk minimisation measures:** EU SmPC section 4.4 EU SmPC section 4.8 PL section 2 PL section 4 Prescription only medicine **Additional Risk Minimisation Measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** A specific follow-up questionnaire is available for this important potential risk ('Immunogenicity_Antibody against treatment drug_v1.0')

Missing Information: Use in Patients with Cardiac Disease	
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional Risk Minimisation Measures:** None

Missing information: Long-term safety in subjects born SGA	
Risk minimisation measures	**Routine risk minimisation measures:** EU SmPC section 4.1

Missing information: Long-term safety in subjects born SGA	
	PL section 1 **Additional Risk Minimisation Measures:** None

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

The following study is condition of the MA:

Study EMR 200098-008 (SALTO)

Study short name: Saizen Long-Term Observational study (SALTO)

Rationale and study objectives:

Rationale:

The study is a PASS and post-approval commitment requested by the Italian health authority (Agenzia Italiana Del Farmaco).

The primary objective of the study is:

- To assess the long-term safety of Saizen up to 10 years after cessation of treatment, in terms of occurrence of Diabetes Mellitus and malignancies, in a minimum of 200 subjects born SGA who were treated with Saizen.

The secondary objectives of the study are:

- To assess occurrence of metabolic syndrome,
- To assess glucose metabolism parameters,
- To characterize the observed malignancies,
- To correlate the occurrence of metabolic syndrome and/or glucose metabolism disorders or malignancy to familial inheritance,
- To correlate the occurrence of metabolic syndrome and glucose metabolism disorders or malignancy to subject characteristics and medical history.

Study population:

- Male and female SGA subjects without age restriction who have permanently discontinued r-hGH / Saizen treatment within 5 years prior to study enrolment.

II.C.2 Other Studies in the Post-authorisation Development Plan

There are no studies required for Saizen.