Zomacton 10 mg/ml powder and solvent for solution for injection

10.9.2015 version 5.0

PUBLIC SUMMARY OF RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Growth hormone deficiency occurs when the pituitary gland does not produce enough growth hormone. Growth hormone deficiency has a variety of different negative effects at different ages; for example, in newborn infants, the primary manifestations may be hypoglycaemia or micropenis, while in later infancy and childhood, growth failure is more likely. Deficiency in adults is rare, but may feature diminished lean body mass, poor bone density, and a number of physical and psychological symptoms. Psychological symptoms include poor memory, social withdrawal, and depression, while physical symptoms may include loss of strength, stamina, and musculature. Other hormonal or glandular disorders frequently coincide with diminished growth hormone production.

The most common causes of GHD (representing two-thirds of cases) are pituitary and parasellar tumors. The origin of adult GHD may be congenital or acquired. Of those adult GHD that are acquired, roughly 15% are idiopathic, 50% are from pituitary tumours, 20% from extrapituitary tumors, and 5% from infiltrative or inflammatory lesions.

Turner syndrome is a genetic condition in females where a part or all of one of the sex (X) chromosomes is missing, sometimes only in a part of the cells in the body. Turner syndrome occurs in 1 in 2000-5000 of live female births. It may be diagnosed by prenatal testing before birth, at birth (due to wide neck or swelling of the hands and feet) or any age (due to short stature or missing pubertal development). One of the characteristic physical abnormalities which affect girls with Turner syndrome is short stature; the adult height is approximately 20 cm below the female average of the ethnic group. Additionally, typical girls with Turner syndrome will have non-working ovaries (leading to lack of menstrual cycles and sterility), and they may have congenital heart disease, hypothyroidism and diabetes mellitus. The severity of these problems varies considerably.

VI.2.2 Summary of treatment benefits

ZOMACTON has been studied in children with

- Growth hormone deficiency (GHD):
  In a recent open-label, randomised, parallel-group, multi-centre, clinical phase 3 study ZOMACTON 1Omg/mL was compared to GENOTROPIN 12mg in terms of clinical safety and efficacy in 165 children with growth hormone deficiency. There were no relevant differences between the two treatments in growth (height gain, height velocity) or safety (adverse events). At Month 12, the adjusted mean height velocity was above 10 cm/year in

both treatment groups.

- Turner syndrome:
  In one study in children with short stature due to GHD, 164 patients started treatment, and the efficacy of the growth hormone treatment was evaluated by monitoring changes in height and weight velocity after 6 and 12 months. After 12 months the increase in height velocity from baseline was 4.4 to 5.7 cm/year (depending on whether the patients had some degree of growth hormone response to stimulation and whether they had previously received growth hormone before the study). Similarly, increase in weight velocity was also seen 1.7 to 2.0 kg/year.

  Another study investigated the growth rates in 98 girls with Turner syndrome, using ZOMACTON for 2 years. The height velocities in the first year were 5.55±1.06 cm/year (low dose) and 6.98±1.63 cm/year (high dose); and in the second year, 4.44±1.24 cm/year (low dose) and 5.28±1.09 cm/year (high dose). This fulfilled the predetermined efficacy criteria for the first year (growth rate $\geq$ 4 cm/year or increase in growth rate $\geq$ 1 cm/year) in 94.4% of patients in the low dose group and 100% in the high dose group.

VI.2.3 Unknowns relating to treatment benefits

There is no data on the effectiveness of ZOMACTON use in elderly.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Antibodies against growth hormone (Anti-somatropin antibodies)	Some patients develop antibodies against growth hormone when treated with somatropin. The level of antibodies is usually low and only in very rare cases do they have impact on the safety or efficacy of the treatment. Often the antibodies have disappeared again during the treatment with growth hormone	Testing for antibodies against growth hormone may be done if there is no effect of growth hormone treatment

Increased pressure around the brain (Benign intracranial hypertension)	**In rare cases increased pressure around** the brain have been reported during somatropin treatment. The symptoms of this can be severe or recurring headache, visual problems, and nausea/vomiting.	In case of severe or recurring headache, visual problems, and nausea/vomiting an examination of the eyes (fundoscopy) to look for papilledema (swelling of the optic disc) should be performed. If papilla oedema is confirmed, somatropin treatment should be discontinued. If treatment with somatropin is restarted, careful monitoring for symptoms of intracranial hypertension is necessary. Gradual dose increase when starting somatropin treatment might eliminate or at least decrease the risk
Diabetes mellitus type II	Somatropin may reduce the body's sensitivity to insulin leading to increased blood sugar (glucose) levels, particularly at higher doses. This can unmask previously undiagnosed impaired glucose tolerance and overt diabetes mellitus	Blood sugar should be monitored periodically, especially in patients with risk factors for diabetes mellitus (obesity, Turner syndrome, or a family history of diabetes mellitus). For patients with diabetes mellitus (type 1 and type 2), the insulin dose may require adjustment after somatropin treatment has started.
Thyroid function impairment	Somatropin may unmask undiagnosed/untreated hypothyroidism (decreased function of the thyroid gland) due to increased conversion of the hormones from the thyroid gland, leading to decreased metabolism	Patients treated with somatropin should have thyroid function monitored periodically and thyroid hormone replacement therapy should be initiated or appropriately adjusted in case of hypothyroidism

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Tumour growth/cancer (Neoplasm)	Somatropin stimulates cell growth and division and there is a theoretical risk that it may stimulate increased growth of abnormal (e.g. malignant) cells. Although there is no clear evidence that somatropin increases the risk of neoplasms, the risk of development of neoplasms should be weighed against the potential benefits of somatropin therapy in each patient Somatropin should not be used in patients with active malignant tumours or tumours inside the brain
Bulge in the wall of a blood vessel in the brain and bleeding in the brain, haemorrhagic stroke (Intracranial aneurysm and intracranial haemorrhage)	Some data indicate that growth hormone can have a beneficial effect on the cardiovascular system, while other data indicate GH may be predisposing to atherosclerotic changes. In one study in mortality due to intracranial bleeding was increased compared to what was suspected compared to the general population, however, some of the underlying conditions causing growth hormone deficiency may in them self be associated with an increased risk of intracranial bleeding.
Seizure (Convulsion)	Seizure has been reported in patients receiving growth hormone. Some of the underlying conditions causing growth hormone deficiency may in themselves be associated with an increased risk of seizures. Seizures may also be associated with the known risk of increased pressure around the brain and possibly with an interaction with medications taken to prevent seizures in patients who already have history of seizures.
Slipped capital femoral epiphysis (SCFE)	Slipped capital femoral epiphysis has been reported in patients receiving growth hormone. Some of the underlying conditions causing growth hormone deficiency may in themselves be associated with an increased risk of SCFE.

Missing information

Risk	What is known
Safety in elderly patients Safety in patients with hepatic or renal impairment, Safety in pregnant/lactating women Safety with long-term use of 5 years	Information is missing

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	03 May 2012	Identified Risks: Anti-somatropin antibodies Benign intracranial hypertension Diabetes mellitus type 2 Potential Risks: Neoplasia Intracranial aneurysm and intracranial hemorrhage	
3.0	02 July 2013	Thyroid function impairment added as a identified risk Convulsions added as potential risk	
4.0	23 Jun 2014		Update to new format
5.0	10 Sep 2015	Slipped capital femoral epiphysis added as potential risk	