5. SUMMARY OF THE EU RISK MANAGEMENT PLAN

Table 23. Overall Summary of the Risk Management Plan for Known Risks

Safety risk	Proposed Pharmaco-vigilance activities (routine and additional)	Risk minimisation activities (routine and additional)
Glucose metabolism impaired		SPC **4.4 Special warnings and precautions for use** Insulin sensitivity Somatropin may reduce insulin sensitivity. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes, glucose intolerance, or additional risk factors for diabetes should be monitored closely during somatropin therapy. Small for gestational age In SGA children it is recommended to measure fasting insulin and blood glucose before start of treatment and annually thereafter. In patients with increased risk for diabetes mellitus (e.g. familial history of diabetes, obesity, severe insulin resistance, acanthosis nigricans) oral glucose tolerance testing (OGTT) should be performed. If overt diabetes occurs, growth hormone should not be administered. **4.8 Undesirable effects** The following undesirable effects have been observed and reported during treatment with Genotropin with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Endocrine disorders: Rare: Diabetes mellitus type II Periodic review per MAH SOPs and cases to be reviewed in PSUR (3 years).

Table 23. Overall Summary of the Risk Management Plan for Known Risks

Safety risk	Proposed Pharmaco-vigilance activities (routine and additional)	Risk minimisation activities (routine and additional)
Thyroid function impaired		SPC **4.4 Special warnings and precautions for use** Thyroid function Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Whereas the peripheral thyroid hormone levels have remained within the reference ranges in the majority of healthy subjects, hypothyroidism theoretically may develop in subjects with subclinical hypothyroidism. Consequently, monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism on standard replacement therapy, the potential effect of growth hormone treatment on thyroid function must be closely monitored. Periodic review per MAH SOPs and cases to be reviewed in PSUR (3 years).
Intracranial hypertension		SPC **4.4 Special warnings and precautions for use** Benign intracranial hypertension In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, the growth hormone treatment should be discontinued. At present there is insufficient evidence to give specific advice on the continuation of growth hormone treatment in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Table 23. Overall Summary of the Risk Management Plan for Known Risks

Safety risk	Proposed Pharmaco-vigilance activities (routine and additional)	Risk minimisation activities (routine and additional)
		4.8 Undesirable effects The following undesirable effects have been observed and reported during treatment with Genotropin with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Nervous system disorders: Rare: Benign intracranial hypertension Periodic review per MAH SOPs and cases to be reviewed in PSUR (3 years).

Table 24. Overall Summary of the Risk Management Plan for Potential Risks

Potential risk	Ongoing and proposed pharmaco-vigilance activities (routine and additional)	Ongoing and proposed risk minimisation activities (routine and additional)
Neoplasias	Routine Pharmacovigilance TME Reviews	SPC **4.3 Contraindications** Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth. **4.4 Special warnings and precautions for use** In growth hormone deficiency secondary to treatment of malignant disease, it is recommended to pay attention to signs of relapse of the malignancy. Leukaemia Leukaemia has been reported in a small number of growth hormone deficiency patients, some of whom have been treated with somatropin. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors. **4.8 Undesirable effects** Very rare cases of leukaemia have been reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency (see Section 4.4). Periodic review per MAH SOPs and cases to be reviewed in PSUR (3 years).

Table 25. Overall Summary of the Risk Management Plan for Potential Risks

Potential risk	Ongoing and proposed pharmaco-vigilance activities (routine and additional)	Ongoing and proposed risk minimisation activities (routine and additional)
Intracranial haemorrhage and intracranial aneurysm	Routine Pharmacovigilance	Based on a review of the database and the literature for this drug class, the risk of intracranial haemorrhage and intracranial aneurysm is mainly theoretical. Therefore, no surveillance measures beyond routine Pharmacovigilance are warranted. Periodic review per MAH SOPs and cases to be reviewed in PSUR (3 years).

Table 26. Overall Summary of the Risk Management Plan for Potential Risks

Safety concerns associated with non-approved uses	Ongoing and proposed pharmaco-vigilance activities (routine and additional)	Ongoing and proposed risk minimisation activities (routine and additional)
Off-Label Use	Routine Pharmacovigilance	SPC lists the approved uses for Genotropin **4.1 Therapeutic Indications** <u>Children</u> Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD) and growth disturbance associated with Turner syndrome or chronic renal insufficiency. 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 SD, who failed to show catch-up growth [height velocity (HV) SDS < 0 during the last year] by 4 years of age or later. Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing. <u>Adults</u> Replacement therapy in adults with pronounced growth hormone deficiency. *Adult Onset*: Patients who have severe growth hormone deficiency associated with multiple hormone deficiencies as a result of known hypothalamic or pituitary pathology, and who have at least one known deficiency of a pituitary hormone not

Table 26. Overall Summary of the Risk Management Plan for Potential Risks

Safety concerns associated with non-approved uses	Ongoing and proposed pharmaco-vigilance activities (routine and additional)	Ongoing and proposed risk minimisation activities (routine and additional)
		being prolactin. These patients should undergo an appropriate dynamic test in order to diagnose or exclude a growth hormone deficiency. *Childhood Onset*: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients with childhood onset GHD should be reevaluated for growth hormone secretory capacity after completion of longitudinal growth. In patients with a high likelihood for persistent GHD, i.e. a congenital cause or GHD secondary to a pituitary/hypothalamic disease or insult, an Insulin-like Growth Factor-I (IGF-I) SDS < -2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of profound GHD. Reports of off-label use will be reviewed in Section 9 of the PSUR every 3 years.