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Assessment report for Somatropin-containing medicinal products

Pursuant to Article 107 of Directive 2001/83/EC, as amended

International Non-proprietary Name: somatropin

Procedure number: EMEA/H/A-107/1287

Procedure under Article 107 of Directive 2001/83/EC, as amended

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 9 December 2010, France circulated a Rapid Alert informing the EMA, the European Commission and the other Member States of concerns on the benefit-risk balance of somatropin-containing medicinal products following data from the French (Santé Adulte Growth Hormone Enfant) SAGHE study suggesting an increased risk of mortality with somatropin therapy.

A procedure under Article 107 of Directive 2001/83/EC, as amended was initiated for somatropin containing medicinal products.

2. Scientific discussion

2.1. Introduction

Somatropin is a recombinant human growth hormone (rhGH) acting on the metabolism of lipids, carbohydrates and proteins. In children with inadequate endogenous growth hormone, somatropin stimulates linear growth and increases growth rate. In adults, somatropin maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilisation of body fat.

Currently there are nine approved somatropin-medicinal products in the Union: Genotropin, Humatrope, Maxomat, Norditropin, Saizen, Zomacton approved via Mutual Recognition procedure (MRP) or Nationally (NAP) and Omnitrope, NutropinAq and Valtropin approved centrally (CAP).

Somatropin (rhGH) products have been available in Europe since the late 1980's for the treatment of several conditions associated with growth hormone deficiency and/or short stature.

In the Union, somatropin is approved to be used in children for growth hormone deficiency (including idiopathic growth hormone deficiency), growth failure in patients with Turner syndrome, chronic renal insufficiency or short stature homeobox-containing gene (SHOX) deficiency, Prader-Willi syndrome and in patients born small for gestational age (SGA). An overview of the therapeutic indications and posology approved for all available products in children in the Union is presented in the following table (Table 1):

Table 1. Therapeutic indications and posology of somatropin containing medicines in the EU

<i>In children</i>	Growth Hormone Deficiency (GHD) (TS)	Turner Syndrome Failure (TSF)	Chronic Renal Failure (CRF)	Small for Gestational Age (SGA)	Prader Willi Syndrome (PAS)	Short stature Homeobox gene (SHOX) deficiency
Genotropin	0.025 – 0.035 mg/kg/day	0.045 – 0.050 mg/kg/day	0.045 – 0.050 mg/kg/day	0.035 mg/kg/day	0.035 mg/kg/day	N/A
Humatrope	0.025 – 0.035 mg/kg/day	0.045 – 0.050 mg/kg/day	0.045 – 0.050 mg/kg/day	0.035 mg/kg/day	N/A	0.045 – 0.050 mg/kg/day
Maxomat	0.025 – 0.035 mg/kg/day	0.035 – 0.045 mg/kg/day	N/A	0.060 mg/kg/day (first 3 years)	N/A	N/A
Norditropin	0.025 – 0.035 mg/kg/day	0.045 – 0.067 mg/kg/day	0.050 mg/kg/day	0.035 mg/kg/day	N/A	N/A

	mg/kg/day	mg/kg/day				
NutropinAq	0.025 – 0.035 mg/kg/day	Up to 0.050 mg/kg/day	Up to 0.050 mg/kg/day	N/A	N/A	N/A
Omnitrope	0.025 – 0.035 mg/kg/day	0.045 – 0.050 mg/kg/day	0.045 – 0.050 mg/kg/day	0.035 mg/kg/day	0.035 mg/kg/day	N/A
Saizen	0.025 – 0.035 mg/kg/day	0.045 – 0.050 mg/kg/day	0.045 – 0.050 mg/kg/day	0.035 mg/kg/day	N/A	N/A
Valtropin	0.025 – 0.035 mg/kg/day	0.045 – 0.050 mg/kg/day	0.045 – 0.050 mg/kg/day	N/A	N/A	N/A
Zomacton	0.020 – 0.030 mg/kg/day	0.050 mg/kg/day	0.047 mg/kg/day	N/A	N/A	N/A

N/A: Not approved

The indications for growth hormone therapy have gradually been extended since the 1980's from severe growth hormone deficiency to a number of conditions in which childhood short stature is not primarily due to a deficiency of endogenous growth hormone secretion. The long term efficacy of somatropin in children with severe growth hormone deficiency is unquestionable.

The safety of growth hormone therapy has been mainly based on large samples of patients followed in post-marketing databases including registries during or not long after treatment only. Therefore, limited information on long-term safety of somatropin treatment is currently available.

Somatropin-treatment has been associated with tumour-promoting potential and this is currently reflected in the product information of all somatropin-containing medicinal products. Firstly due to the biological plausibility based on the established tumorigenic potential of insulin-like growth factor-1 (IGF-1), which is the key mediator of GH activity and secreted in response to GH receptor activation. Secondly, due to several published studies that reported a higher risk of tumour and/or tumour related mortality for patients treated with growth hormone (Swerdlow et al. 2002¹, Sklar et al. 2002² and by Ergun-Longmire et al. 2006³).

In fact this safety issue of tumour-promoting potential was subject to a review performed by the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) which concluded, in early 2009 that changes to the labelling were strongly recommended. It was also acknowledged that the risk assessment performed was based in a small number of cases and the significance of these results would still remain uncertain until further data was available.

A large epidemiological study based on data from the Association France-Hypophyse registry was ongoing since 2007 – the French Santé Adulte GH Enfant (SAGHE) study. This long-term surveillance study collected data from all patients that were treated with rhGH in the period from 1985 to 1996 and who were older than 18 years of age at the time of data collection in 2007. The primary objective of

¹ Swerdlow AJ, Higgins CD, Adlard P, et al. Risk of cancer in patients treated with pituitary growth hormone in the UK, 1959-85: a cohort study. *Lancet* 2002; 360:273-277.

² Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: A report from the Childhood Cancer Survivor Study. *J. Clin. Endocrinol. Metab.* 2002;87:3136-3141

³ Ergun Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W et al. Growth hormone treated and risk of second malignant neoplasms in the childhood cancer survivor. *J Clin Endocrinol Metab* 2006;91:3494-3498

the study was to evaluate the overall and cancer-related mortality and morbidity risks in comparison with risks in the general population.

On 9 December 2010, the French National Competent Authority (AFSSAPS) informed the European Commission, the European Medicines Agency and all Member States of unpublished results of the SAGHE study that showed an all-cause mortality significantly higher in children treated with rhGH (Standardised Mortality Ratio - SMR 1.33, 95% CI 1.08; 1.64). These results suggested an increased mortality with doses higher than 0.050 mg/Kg/day and due to diseases of the circulatory system (subarachnoid or intracerebral haemorrhage) and bone tumours.

This information was circulated in a rapid alert triggering a procedure under Article 107 of Directive 2001/83/EC, as amended. There were concerns on the impact of the results of this study on the benefit-risk balance of somatotropin-containing medicinal products.

During its plenary meeting in December 2010, the results of the SAGHE study were presented by the principal investigator to the PhVWP and to the CHMP.

On 16 December 2010 the CHMP initiated the procedure under Article 107 for all somatotropin-containing medicinal products: a list of questions to be addressed by the concerned Marketing Authorisation Holders (MAHs) of all somatotropin-containing medicinal products and a list of question to be addressed by the investigators of the French SAGHE study were adopted.

All safety data submitted to this review was considered by the CHMP and is hereafter discussed.

2.2. Clinical safety

Safety data were submitted by the MAHs, including data from clinical trials (past and ongoing), registries, cohorts and safety databases (pharmacovigilance) on risk of neoplasms and cardiovascular risks. Data available in the literature on these issues were also considered. In addition the EMA provided data from the European Pharmacovigilance database (Eudravigilance) and conducted a drug utilisation study of somatotropin-containing products in the United Kingdom by using the THIN database.

2.2.1. French Santé Adulte GH Enfant (SAGHE) study

Design and objectives

This is a long-term surveillance study which collected data from a mandatory register in France of all patients that were treated with rhGH during childhood between the period of 1985 to 1996 and who were older than 18 years of age at the time of data collection in 2007. Follow-up data were collected from paediatric endocrinologists until 1996 and additional follow-up data were collected from clinical centres in 2008-2010.

The primary objective was to evaluate the overall and cancer-related mortality and morbidity risks in comparison with the risks in the general population. Secondary objectives were to assess the non-cancer mortality and morbidity risks on an exploratory basis.

Study population

All 10,330 patients that were treated with rhGH and who were older than 18 years by the end of 2007 were assigned to three risk categories for long-term mortality based on the clinical condition.

The low risk population defined as treatment for idiopathic growth hormone deficiency, idiopathic short stature, short stature in children born short for gestational age, or isolated growth hormone deficiency was included in the mortality analysis (n=6,892 patients corresponding to 116,403 person-years of observation).

All other categories of growth hormone treated children were excluded from this analysis, including those with multiple pituitary hormone deficiency, growth hormone deficiency secondary to a tumour and syndromes such as Turner syndrome.

Results

The mean follow-up time from treatment initiation to death, loss to follow-up or census was 16.9 years. The principal outcomes measured were standardised mortality ratios (SMR) and hazard ratios (HR, using the category with the lowest exposure level as the reference).

All-cause mortality was higher in children treated with growth hormone (SMR 1.33, 95% CI 1.08–1.64) in comparison with general population (Table 2). Mortality was significantly higher for the children who were shortest at the start of treatment and those who received the highest doses of growth hormone. An increased risk was also associated with the short duration of treatment.

Table 2. Mortality analysed by mean rhGH dose, by treatment duration and by overall exposure

	Observed	Expected	SMR	(95% CI)
Overall	93	69.67	1.33	(1.08 - 1.64)
Mean growth hormone dose (µg/kg/day)				
0 - 20 (n = 2277)	32	29.77	1.07	(0.74 - 1.52)
20 - 30 (n = 3195)	35	29.07	1.20	(0.84 - 1.67)
30 - 50 (n = 580)	5	3.54	1.41	(0.46 - 3.30)
>50 (n = 281)	6	1.76	3.41	(1.25 - 7.42)
			<i>P trend 0.04</i>	
Treatment duration (years)				
0 - 2 (n = 1467)	29	15.87	1.83	(1.22 - 2.62)
2 - 4 (n = 2650)	36	29.72	1.21	(0.85 - 1.68)
>4 (n = 2285)	26	21.12	1.23	(0.80 - 1.80)
			<i>P trend 0.17</i>	
Overall exposure (mg/Kg)				
<16 mg/Kg (n=1381)	22	17.03	1.29	(0.81 - 1.96)
16.0 – 27.0 mg/Kg (n=1524)	17	17.97	0.95	(0.55 - 1.51)
27.0 – 47.0 mg/Kg (n=1543)	17	15.52	1.10	(0.64 - 1.75)
≥47.0 mg/Kg (n=1427)	20	10.86	1.84	(1.13 - 2.84)
			<i>P trend 0.32</i>	

When adjusted for height at the start of treatment, the use of doses higher than 0.050 mg/kg/day was significantly associated with mortality (adjusted SMR 2.94, 95%CI 1.22–7.07, adjusted HR 2.79, 95%CI 1.14–6.82).

Analyses by specific cause of mortality showed an increase due to diseases of the circulatory system (SMR 3.07, 95%CI 1.40–5.83), bone tumours (SMR 5.00, 95%CI 1.01–14.63) and subarachnoid or intracerebral haemorrhage (SMR 6.66, 95%CI 1.79–17.05). Table 3 (below) shows the SMR of rhGH treated patients by ICD category.

Table 3. Mortality analysed by ICD category

	Observed	Expected	SMR	(95%CI)
Infectious and parasitic diseases	3	1.05	2.86	(0.57 - 8.35)
Neoplasms	7	6.89	1.02	(0.41 - 2.09)
Endocrine, nutritional and metabolic diseases, and immunity disorders	2	0.31	6.50	(0.73 - 23.46)
Diseases of the blood and blood-forming organs	1	0.88	1.13	(0.01 - 6.30)
Mental disorders	1	1.32	0.75	(0.01 - 4.20)
Diseases of the nervous system and sense organs	3	2.71	1.11	(0.22 - 3.24)
Diseases of the circulatory system	9	2.93	3.07	(1.40 - 5.83)
Diseases of the respiratory system	2	1.08	1.85	(0.21 - 6.66)
Diseases of the digestive system	-	0.48	-	
Diseases of the genitourinary system	-	0.02	-	
Complications of pregnancy, childbirth, and the puerperium	-	0.14	-	
Diseases of the skin and subcutaneous tissue	-	0.12	-	
Diseases of the musculoskeletal system and connective tissue	-	0.09	-	
Congenital anomalies	-	0.01	-	
Certain conditions originating in the perinatal period	1	1.14	0.88	(0.01 - 4.90)
Symptoms, signs, and ill-defined conditions	21*	6.28	3.35	(2.07 - 5.11)
Injury and poisoning	43	44.22	0.97	(0.70 - 1.31)
Neoplasms	7	6.89	1.02	(0.41 - 2.09)
Malignant neoplasm of lip, oral cavity, and pharynx	1	0.10	9.64	(0.13 - 53.62)
Malignant neoplasm of lymphatic and haematopoietic tissue	2	1.36	1.47	(0.17 - 5.32)
Malignant melanoma of skin	1	0.24	4.14	(0.05 - 23.02)
Malignant neoplasm of bone and articular cartilage	3	0.60	5.00	(1.01 - 14.63)
Diseases of the circulatory system	9	2.93	3.07	(1.40 - 5.83)
Other disorders of circulatory system	1	0.66	1.53	(0.02 - 8.49)
Other heart diseases	4	1.19	3.37	(0.91 - 8.64)
including cardiomyopathy and cardiomegaly	2	0.28	7.11	(0.80 - 25.67)
Cerebrovascular disease	4	0.76	5.29	(1.42 - 13.55)
including subarachnoid haemorrhage, intracerebral haemorrhage and other non-traumatic intracranial haemorrhages	4	0.60	6.66	(1.79 - 17.05)

Discussion and conclusion

Overall, results of the French SAGHE study suggest a small increased mortality risk with an excess of 23 deaths over the 70 expected.

The suggested increased risk with the dose is only statistically significant in the group treated with mean doses above 0.050 mg/kg/day (n=281, table 2). In this group, 225 (80%) out of the 281 patients were part of a company-sponsored study conducted in children born short for gestational age (SGA). A sensitive analysis of survival excluding these SGA patients showed a dose effect (HR of 5.05 [1.16-22.09]) with a threshold of 0.040 mg/kg/day (dose range 0-0.020 mg/kg/day as reference). Therefore, the dose effect of GH treatment in this patient group may not only be due to patients who

were born SGA. Nevertheless, this is a very small population for a clear association with the dose to be made.

In addition, the analysis of mortality by cumulative dose does not show a dose effect.

The statistically significant increased risk seen only for patients treated for less than 2 years could not be explained.

Of the 93 all-cause mortality cases, 21 deaths classified as resulting from "ill-defined conditions" are noted to be of unknown cause. Data from the patient group that died due to diseases of the circulatory system (n=9) showed that all but one had been treated for a diagnosis of growth hormone deficiency. Age at death was between 13 and 33 years old and all deaths except one occurred between 13 and 17.8 years old after treatment initiation. No information on the presence of cardiovascular risk factors was available for 3 patients. This information is very limited not allowing a conclusion.

No data on the occurrence of non-fatal neoplasms in patients of the SAGHE study is, at the moment, available. The morbidity study planned in the scope of the French SAGHE study is currently on-going.

Finally, one of the main limitations of this study is the general population that was used as reference group to calculate the SMR. This leads to unmeasurable confounding that precludes the results of this study to be regarded as robust evidence. Moreover the characteristics of the treated patients may per se be associated with increased mortality even if in a low risk group (isolated GHD, ISS and SGA).

Based on all the above, the results currently available from this large and long-term study cannot be regarded as robust. Nevertheless, these results are regarded as potential safety signal to be further considered upon availability of additional long-term safety data.

2.2.2. European Santé Adulte GH Enfant (SAGHE) study

The French SAGHE study is part of an European consortium called "SAGHE" for safety and appropriateness of growth hormone treatment in Europe, involving other 7 countries (Belgium, United Kingdom, Netherlands, Switzerland, Italy, Germany and Sweden) which started on the 1st of June 2009. This study is part of the FP7 Health work programme and approximately the sample size is of 30,000 patients. The study results are expected to be available in 2013.

The investigators of the SAGHE in each involved country were invited to share preliminary available data on the association between GH treatment in childhood and mortality (overall and cancer-related) and cancer incidence (overall and cancer specific) from their cohorts. However, the process of collecting data from national registries on GH-treated children is still on going and no data was available for this review.

2.2.3. Data from clinical studies, registries, cohorts and safety databases

Exposure data by indication and dose (mg/Kg/day) was submitted for almost all somatotropin medicinal products based on their ongoing registries. Stratification by country was also submitted when available. Overall the higher exposure of use of somatotropin in Europe is shown in idiopathic growth hormone deficiencies and in general used within the range of recommended doses. All products have a registry in place and only one of the nine somatotropin products has not been marketed.

Data from clinical trials (past and ongoing), registries, and cohorts were submitted by the MAHs addressing the two main safety concerns of neoplasms and cardiovascular/cerebrovascular risks.

Overall, no conclusion can be drawn on the risks observed from these data. The clinical studies have short duration, the follow-up is predominately performed during treatment or during 3- 4 years after treatment and the number of patients is very limited for a powerful statistical analysis to be performed.

Cumulative reviews from post-marketing data were also performed and presented by the MAHs. Overall, no safety concern regarding fatal cardiovascular events and fatal *de novo* malignancies or recurrence of malignancies in rhGH treated patients with a prior history of cancer rise from these data.

2.2.4. Literature review data

Baseline Mortality and Morbidity

In the vast majority of studies available on patients with Growth Hormone Deficiency (GHD), all-cause mortality is increased in patients with hypopituitarism when compared to age- and sex-matched controls⁴ (SMR = 1.81 p<0.001, with an average follow up duration of 15.2 years). Mortality due to vascular or cardiovascular events was particularly of concern in these patients⁵.

GH deficiency has been associated with cardiovascular risk factors: abnormal body composition, excess body fat, elevated waist-to-hip ratio and BMI, dyslipidemia, hyperinsulinemia, elevated inflammatory markers and hypertension, premature atherosclerosis in several studies. (^{6, 7, 8, 9, , 10}).

In patients born Small for Gestational Age (SGA) and patients with Idiopathic Short Stature (ISS), a meta-analysis by *Paajanen and col.* (¹¹) reported that "*All cause mortality*" as well as "*Cardiovascular mortality*" is inversely proportional to height, with the shortest individuals having the highest risk. Several other studies also reported that children with ISS or SGA are more prone to develop metabolic and cardiovascular risk factors (^{12, 13, 14, 15}).

⁴ Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990; 336(8710):285-8.

⁵ Sherlock M, Ayuk J, Tomlinson JW, et al. Mortality in patients with pituitary disease. *Endocr Rev* 2010; 31(3):301-42.

⁶ Abs R, Feldt-Rasmussen U, Mattsson AF, et al. Determinants of cardiovascular risk in 2589 hypopituitary GH- deficient adults - a KIMS database analysis. *Eur J Endocrinol* 2006; 155(1):79-90.

⁷ Fideleff HL, Boquete HR, Staldecke G, et al. Comparative results of a 4-year study on cardiovascular parameters, lipid metabolism, body composition and bone mass between untreated and treated adult growth hormone deficient patients. *Growth Horm IGF Res* 2008; 18(4):318-24.

⁸ Juul A, Scheike T, Davidsen M, et al. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case-control study. *Circulation* 2002; 106(8):939-44.

⁹ Markussis V, Beshyah SA, Fisher C, Sharp P, et al (1992) Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet*; 340:1188-92.

¹⁰ Verhelst J, Abs R. Cardiovascular risk factors in hypopituitary Ghdeficient adults. *Eur J Endocrinol* 2009; 161(Suppl 1):S41-9.

¹¹ Paajanen TA, Oksala NK, Kuukasjärvi P, Karhunen PJ. Short stature is associated with coronary heart disease: a systematic review of the literature and a meta-analysis. *Eur Heart J.* 2010; 31(14):1802-9.

¹² Bechtold S and Pozza RD, Bonfig W, Putzker s, Weissenbacher C, Schwarz HP. Cardiovascular risk factors in short children born SGA treated with growth hormone (P2-d1-509). Presented at the ESPE 49th Annual Meeting, 22-25 September 2010.

¹³ De Arriba A, Labarta JI, Domínguez M. et al. Study of early markers of cardiovascular disease in patients born small for gestational age (P2-d1-513). Presented at the ESPE 49th Annual Meeting, 22-25 September 2010.

¹⁴ Meas T, Deghmoun S, Armoogum P et al. Consequences of Being Born Small for Gestational Age on Body Composition: An 8-Year Follow-Up Study. *J. Clin. Endocrinol. Metab.* 2008 93:3804-3809

¹⁵ Petrova M and Bolotova N. Cardiovascular system peculiarities in children with growth hormone deficiency and idiopathic short stature (P1-d3-342). Presented at the ESPE 49th Annual Meeting, 22-25 September 2010.

Mortality/morbidity in GH-treated patients

It has been shown that all-cause mortality rate is not different from the normal population rate (¹⁶).

Growth hormone treatment in paediatric and adult GHD-patients has not demonstrated any deleterious effect on various concomitant cardiovascular risk factors. It is noted that beneficial effects of GH treatment on several cardiovascular risk factors such as lipids and blood pressure, and consequently a potential reduction in cardiovascular and vascular morbidities have been reported. There are currently no data to support a negative impact of GH treatment in terms of cardiovascular risk. Nevertheless, this potential risk should be considered during the treatment with somatropin.

GH therapy neither increases the recurrence of childhood neoplasms nor the overall incidence of *de novo* cases. The recurrence of tumours or the occurrence of second neoplasms are mainly observed in high risk patients who have been previously treated by radiotherapy and/or chemotherapy and received in addition GH treatment for short stature due to their pathology. This higher risk of a 2nd neoplasm reported in childhood cancer survivors treated with somatropin has been described by *Sklar et al* (2002) and Ergun-Longmire(2006) and is reflected in the product information of some somatropin products. However, the majority of data has been obtained in children and in adults under treatment or shortly after GH treatment discontinuation. Hence there is a significant lack of long term safety data on adults treated with GH during childhood. The cohort study of *Swerdlow et al* in the UK was unique in providing data on mortality with a mean follow-up of 21 years, but in a limited number of patients.

2.2.5. Data provided by the EMA

The Pharmacovigilance and Risk Management section of the EMA performed an analysis of the case reports received up to 7th December 2010 with recombinant growth hormone and included in the Eudravigilance database. Overall a total of 5044 case reports (EEA case reports=1998; reports in patients <18 years=2773) of which 446 with fatal outcome were identified. Information regarding dose-effect and fatal outcome was too limited and too heterogeneous to be exploitable. Therefore, no conclusion can be drawn on a relationship between deaths and the GH doses used.

The use of somatropin in clinical practice in the UK was characterised in a drug utilisation analysis of the Health Improvement Network (THIN) database. This study provided an overview of the pattern of utilisation of somatropin-containing products in the UK with regards to age, sex and indications. Data on doses are not interpretable due to the incomplete information regarding weight.

2.3. Overall assessment and conclusion

Somatropin medicinal products in the Union are approved to be used in children for growth hormone deficiency (including idiopathic growth hormone deficiency), growth failure in patients with Turner syndrome, chronic renal insufficiency or short stature homeobox-containing gene (SHOX) deficiency, Prader-Willi syndrome and in patients born small for gestational age (SGA). Some indications are not approved for all somatropin containing medicines.

¹⁶ Gaillard RC, Mattsson AF, Koltowska-Haggstrom M, et al. IGF-I during GH Replacement Therapy Is an Independent Factor Associated with Reduced Mortality in Adult GH Deficient Patients: Results from KIMS (Pfizer International Metabolic Database). Presented at the 90th annual meeting of the Endocrine Society, San Francisco CA, June 13-15, 2008.

The long term efficacy of somatropin in children with severe growth hormone deficiency is unquestionable. Long term safety data on adults treated with growth hormone during childhood is based on large samples of patients followed in post-marketing databases during or not long after treatment. Therefore, long term safety data of somatropin treatment is limited.

Somatropin-treatment has been associated with potential tumour-promoting not only due to the biological plausibility based on the established tumorigenic potential of insulin-like growth factor-1 (IGF-1) but also due to several published studies that reported a higher risk of tumour and/or tumour related mortality for patients treated with growth hormone (Swerdlow et al. 2002, Sklar et al. 2002 and by Ergun-Longmire et al. 2006). This potential risk associated with the growth hormone treatment is reflected in the product information for all somatropin-containing products.

Results of the French SAGHE study, a long-term surveillance study in a high number of patients and with a mean follow up of 17 years suggested an overall increase of mortality in patients treated with somatropin for isolated growth hormone deficiency (GDH), idiopathic short stature (ISS) and short for gestational age (SGA) compared to the general population. Increased mortality was apparent when higher doses were used and due to subarachnoid or intracerebral haemorrhage and bone tumours.

However, this study presents significant methodological limitations that preclude these results to be regarded as robust. Namely, the general population used as reference group for the calculation of the standard mortality ratios leading to unmeasurable confounding. Also, the characteristics of the treated patients that *per se* may be associated with increased mortality, even if in a low risk group (i.e. treated for isolated GHD, ISS and SGA).

Overall mortality risk was small, with an excess of 23 deaths over the 70 expected. Of the 93 all-cause mortality cases, 21 classified as resulting from "ill-defined conditions" are of unknown cause. The suggested increased risk with the higher doses is only statistically significant in the group treated with mean doses above 50 µg/kg/day (n=281). It is noted that in this group, 225 (80%) patients were part of a company-sponsored study conducted in children born short for gestational age (SGA) and overall this is considered a very small subpopulation for a clear association of the suggested risk with the dose. In addition the risk increased with short duration of treatment, nevertheless a sub-analysis by cumulative doses did not confirm this finding. Finally, data from the patient group that died due to diseases of the circulatory system showed that all but one had been treated for a diagnosis of growth hormone deficiency. No information on the presence of cardiovascular risk factors was available for 3 out of 9 patients. This information is very limited not allowing a conclusion with regards the cardiovascular risks.

No data on the occurrence of non-fatal neoplasms in patients of the SAGHE study is, at the moment, available and the morbidity results are still on-going.

The CHMP reviewed all data available from clinical trials (past and ongoing), registries, cohorts and safety databases (pharmacovigilance) on risk of neoplasms and cardiovascular risk provided by the MAHs. Overall, no conclusion can be drawn on the risks observed from these data. The short duration of the studies and the follow-up which is predominately performed during treatment or for 3- 4 years after treatment and the number of patients is very limited for a powerful statistical analysis to be performed.

Data available from the literature was also reviewed. No new or additional safety concern rise from new published data.

Overall, in view of the limitations of the French SAGHE study the findings of an apparent increased risk of mortality in children treated with somatropin (increased risk with higher doses and relating to subarachnoid or intracerebral haemorrhage and bone tumours) cannot be regarded as robust data.

However, the results of the French SAGHE study are regarded as potential safety signal to be further considered in light of long term safety data that will become available in 2 years time, namely the results of the European SAGHE consortium study. In the meantime and based on all above discussed, the Committee considered justified to harmonise already existing contraindications for all somatropin containing medicinal products with regards the potential for tumour-promoting associated with treatment. A specific wording to be include in section 4.3 of the SmPCs and reflected in the package leaflet of all somatropin-containing medicinal products was agreed (see section 2.5).

This potential risk should also be reflected in the Risk Management Plan for all somatropin products as well as the potential risk to subarachnoid or intracerebral haemorrhage.

Finally, to address the potential signal of an increased risk with increased dose as suggested by the results of the French SAGHE study, it was agreed to emphasize in the product information of all somatropin-containing medicinal products that the maximum recommended daily dose should not be exceeded.

2.4. Risk management plan

In view of the above discussed and considering that results of the French SAGHE study are regarded as potential safety signal, the CHMP concluded that the Risk Management Plans of all somatropin containing medicinal products should be submitted/updated to reflect the following potential risks:

- New neoplasm
- Second neoplasm in childhood cancer survivors
- Intracranial aneurysm and Intracranial haemorrhage

2.5. Changes to the product information

In light of the above concluded the CHMP agreed with the following amendments to the product information of all somatropin-containing medicinal products:

Summary of Product Characteristics

[...]

Section 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."

[...]

Section 4.4 "Special warnings and precautions for use"

"The maximum recommended daily dose should not be exceeded (see section 4.2)."

[...]

Package Leaflet

[...]

2. Before you use <(Invented) name of the product>

Do not use <(Invented) name of the product> and tell your doctor if you have an active tumour (cancer). Tumours must be inactive and you must have finished your anti-tumour treatment before you start your treatment with <(Invented) name of the product>.

3. Overall conclusion

Having considered the overall submitted data provided in writing namely the results of the French SAGHE study and data from clinical trials, registries, cohorts and safety databases submitted by the MAHs, the CHMP concluded that:

- the French SAGHE study has significant methodological limitations (e.g. general population used as reference for the calculation of mortality). In view of these limitations, the Committee agreed that the study findings of an apparent increased risk of mortality in children treated with somatropin (increased risk with higher doses and relating to subarachnoid or intracerebral haemorrhage and bone tumours) cannot be regarded as robust;
- other data reviewed did not corroborate the results of the SAGHE study, or provided additional safety concerns;
- however, the results of the French SAGHE study are regarded as potential safety signal. Considering previously published data and information already included in the Product Information for some somatropins, the Committee considered that it is justified to harmonise existing contraindications for all somatropin containing medicines when there is any evidence of activity of a tumour. This also needs to be reflected in the Risk Management Plans as well as the potential risk linked to subarachnoid or intracerebral haemorrhage. Furthermore, the Committee agreed to emphasise in the Product Information (section 4.4) the need for the maximum recommended dose not to be exceeded.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisations for the medicinal products referred to in Annex I of the Opinion, for which amendments to the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion.

The conditions affecting the marketing authorisations are set out in Annex IV of the Opinion.