Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Humatrope

(somatropin)

NL/W/0007/pdWS/004

Marketing Authorisation Holder: Lilly Deutschland GmbH

Rapporteur:	The Netherlands
Finalisation procedure (day 120):	10 January 2018

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Humatrope
INN (or common name) of the active substance(s):	somatropin
MAH:	Lilly Deutschland GmbH
Currently approved Indication(s)	**Paediatric Patients** Humatrope is indicated for the: • long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous GH • treatment of short stature in children with Turner syndrome, confirmed by chromosome analysis • treatment of growth retardation in prepubertal children with chronic renal insufficiency • treatment of patients who have growth failure associated with SHOX deficiency, as confirmed by DNA analysis • growth disturbance (current height 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 SDS <0 during the last year) by 4 years of age or later. **Adult Patients** Humatrope is indicated for replacement therapy in adults with pronounced growth hormone deficiency. Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low IGF-I concentrations <-2 SDS who may be considered for one test. The cut-off point of the dynamic test should be strict.
Pharmaco-therapeutic group (ATC Code):	Anterior pituitary lobe hormones and analogues (H01AC01)
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection 6 mg, 12 mg and 24 mg

List of abbreviations

ASMF	Active Substance Master File
CA	Chronological age
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CRI	Chronic Renal Insufficiency
CVD	Cerebrovascular Disease
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FH	Final Height
GeNeSIS	Genetics and Neuroendocrinology of Short Stature International Study
GH	Growth Hormone
GHD	Growth Hormone Deficiency
Ht	Height
HYPOCCS	Hypopituitary Control and Complications Study
ICH	International Conference of Harmonisation
IGF	Insulin-like Growth Factor
ISS	Idiopathic Short Statue
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUSA	Periodic Safety Update Single Assessment
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAGhE	Safety and Appropriateness of Growth hormone treatments in Europe
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for Gestational Age
SHOX-D	Short Stature Homeobox-containing Gene Deficiency
SIR	Standardised Incidence Ratios
SmPC	Summary of Product Characteristics
SMR	Standardised Mortality Ratios
TEAE	Treatment emergent adverse event
TS	Turner Syndrome
TSE	Transmissible Spongiform Encephalopathy

I. EXECUTIVE SUMMARY

SmPC changes are proposed.

II. RECOMMENDATION

Based upon the submitted final long term efficacy data on final height gain in paediatric patients treated with somatropin in the approved indications, changes to the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) are considered necessary. Moreover, the safety outcomes of the study, with almost 20 years of real life available data at this stage, should also be reflected in the SmPC taken into account the limitations of the study.

III. INTRODUCTION

On 3 November 2017, the Marketing Authorisation Holder (MAH) submitted a the final study report of the paediatric study B9R-EW-GDFC, also known as GeNeSIS (The Genetics and Neuroendocrinology of Short Stature International Study), for Humatrope (somatropin). The final study report is in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A clinical overview has been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Humatrope (somatropin) for its approved indications and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Within study B9R-EW-GDFC the currently marketed product is used.

IV.2 Clinical aspects

IV.2.1. Introduction

The MAH submitted a final report for:

- B9R-EW-GDFC, also known as GeNeSIS, The Genetics and Neuroendocrinology of Short Stature International Study

IV.2.2. Clinical study

- **Description**

This study, which started in 1999 and ended in 2013, collected information on the clinical management and treatment outcomes of paediatric patients with growth disorders who were treated with somatropin according to standard paediatric endocrine practice.

- **Methods**

  - **Objectives**

  The overarching goal of this study was to evaluate the safety and effectiveness of somatropin treatment based on data collected in an observational setting.

Two co-primary safety objectives were:
1. Incidence of type 2 diabetes mellitus in somatropin-treated children;
2. Incidence of de novo neoplasia in somatropin-treated children without a prior history of neoplastic disease

The primary effectiveness objective was to optimise outcome in somatropin-treated patients by identifying factors associated with final height (FH).
Secondary objectives, including outcomes from the core and the substudies, were:
- To characterise genetic defects and DNA sequence alterations associated with hypopituitarism, growth hormone deficiency (GHD), growth disorders or short stature.
- To develop and validate accurate growth prediction models using clinical data (auxologic parameters, bone age and biochemical/genetic data (e.g. insulin-like growth factor-1 and insulin-like growth factor binding protein-3, urinary bone markers and relevant genetic markers).
- To characterise the clinical, endocrine, and other features associated with short stature homeobox-containing gene deficiency (SHOX-D) and related disorders including Turner syndrome, Léri-Weill syndrome, and Langer syndrome.
- To characterise the natural history of neoplastic disease, especially in relation to recurrence/progression of primary neoplasia or development of secondary neoplasia in children with a history of neoplasia evaluated or treated for an endocrine disorder or a growth disorder.
- To examine the occurrence of de novo neoplasia's in both somatropin-treated and untreated patients
- To examine the risk of diabetes mellitus or conditions associated with alterations in glucose metabolism in particular subgroups of somatropin-treated children.

- **Study design**

GeNeSIS was an open-label, multicentre, multinational, observational study, established as a post-authorisation safety study. The global GeNeSIS programme included a 'core study' in which all patients were enrolled, that addressed the primary objectives of safety and effectiveness of somatropin treatment. Four optional substudies included specific patient subgroups that were of additional interest to the paediatric endocrine community. These were the Genetic Analysis, Growth Prediction, SHOX-D and Neoplasia substudies. The Neoplasia and SHOX-deficiency substudies also invited participation of patients not treated with somatropin. Depending on local factors certain substudies were not implemented in specific countries. Data collection for the proposed fifth substudy on abnormal glucose metabolism was included in protocol amendment.

- **Study population/Sample size**

A total of 22,845 patients were enrolled (22,311 treated, 457 untreated, 77 unknown therapy group) from 827 sites in 30 countries.

Discontinuation from the study in the somatropin-treated population was primarily due to sponsor decision including close of the study (25%), attainment of FH (24%) and being lost to follow-up (17%), see table below.

Table 1: Summary of reasons for discontinuation from GeNeSIS

GeNeSIS Discontinuation Summary	Treated n (%)	Untreated n (%)	Unknown n (%)
All enrolled	22311	457	77
Patients who have not completed GeNeSIS summary	4360	64	22
Patients who have completed GeNeSIS summary	17951 (100%)	393 (100%)	55 (100%)
SPONSOR'S DECISION(STUDY OR PATIENT DISCONTINUED BY SPONOR)	4467 (24.88%)	79 (20.10%)	23 (41.82)
FINAL HEIGHT ATTAINED, NO FURTHER FOLLOW-UP PLANNED	4249 (23.67%)	21 (5.34%)	5 (9.09%)
UNABLE TO CONTACT PATIENT (LOST TO FOLLOW-UP)	3052 (17.00%)	130 (33.08%)	11 (20.00%)
OTHER[1]	2089 (11.64%)	103 (26.21%)	9 (16.36%)
PATIENT/PARENT DECISION	1761 (9.81)	25 (6.36%)	1 (1.82%)
PHYSICIAN DECISION	1041 (5.80%)	8 (2.04%)	4 (7.27%)

PATIENT MOVED	601 (3.35%)	21 (5.34%)	2 (3.64%)
THIRD PARTY REQUIRED PATIENT TO CHANGE BRAND OF GH[2]	487 (2.71%)	0	0
PATIENT HAS RECEIVED ANOTHER GH PRODUCT FOR OVER 1 YEAR[3]	79 (0.44%)	0	0
PATIENT TRANSFERRED TO HYPOCCS STUDY	45 (0.25%)	0	0
DEATH	42 (0.23%)	6 (1.53%)	0
ADVERSE EVENT	38 (0.21%)	0	0

Abbreviations: GH = growth hormone; HYPOCCS = Hypopituitary Control and Complications Study.
Note: Only reasons with non-missing visits were considered in the table. In case patients had multiple reasons for discontinuation only the latest reason for visit was used in the table.
[1] Reasons for discontinuation, including "Other" were collected by checkbox entries, a free-text write in field was provided to specify reason, but detailed analysis of the specified reasons is not available.
[2] Amendment of the GeNeSIS protocol allowed patients who were switched to another somatropin brand to remain in the study indefinitely. However, many patients still discontinued the study after a switch to another GH brand.
[3] Prior to the implementation of amendment patients were allowed to remain in the study after switching to another somatropin brand for up to 1 year.

- **Treatments**

Somatropin was administered by subcutaneous injection. Due to the observational nature of the study, all decisions regarding somatropin treatment (including but not limited to: initiation, dosage, injection frequency, changes to regimen, concomitant medications and treatment discontinuation) were solely at the discretion of the investigator and the patient and/or patient's parent(s)/guardian(s). The MAH did not provide the investigational product (somatropin). At initiation of the study in 1999, inclusion criteria required that GH-treated patients be treated with Humatrope. During the course of the study allowance was first made for short term switches to other brands of somatropin for periods of up to 1 year and then subsequently permanent switches were allowed.

The GeNESIS database contains 3 principal treatment groups:
- *Previously treated*: patients who received somatropin treatment before entry in GeNeSIS. Note: no follow-up data are available until entry in GeNeSIS.
- *Naïve*: patients who have never received somatropin treatment before entry in GeNeSIS; however, they received somatropin treatment after entry (naïve, treated) or are supposed to start somatropin treatment within 1 year after entry. Note: regularly collected efficacy follow-up data since start of GH treatment are available for these patients only.
- *Nontreated*: patients who had never received somatropin treatment and were not expected ever to receive somatropin treatment.

- **Outcomes/endpoints**

Two co-primary safety outcomes were:
1. Incidence of type 2 diabetes mellitus in somatropin-treated children;
2. Incidence of de novo neoplasia in somatropin-treated children without a prior history of neoplastic disease.

Other safety outcomes addressed in the study protocol were incidence of second neoplasms and recurrence of primary neoplasms, and development of abnormal glucose metabolism. In addition, publications from the French cohort of the Safety and Appropriateness of Growth hormone treatments in Europe (SAGHE) study had raised concerns of increased mortality and incidence of haemorrhagic stroke in selected somatropin-treated patients groups. Therefore, assessments of mortality and cardiovascular disease were also included as key analyses.

The primary effectiveness objective was to optimise outcome in somatropin-treated patients by identifying factors associated with final height.

- **Statistical Methods**

Safety
Diabetes mellitus: calculation of standardised incidence ratios (SIR)
The SIRs for type 1 and type 2 diabetes mellitus were calculated as the ratio between cases observed in GeNeSIS and expected number of cases based on incidence reported in the search for Diabetes in

youth reference population, stratified by age and ethnicity. The observed number of diabetes cases was assumed to follow a Poisson distribution, and exact 2-sided 95% confidence interval (CI) were calculated.

Primary cancer: calculations of SIR
SIRs and associated 95% CIs for all-sites primary cancer were determined by country, as the ratio between the number of cases observed in GeNeSIS and the expected number of incident cases based on country-, gender-, race-, age-, and calendar year-specific cancer incidence rates for the US general population from the SEER programme (SEER 2014) or country, gender- and age-specific cancer incidence rates for the general population from GLOBOCAN for all other countries (Ferlay et al. 2013). Country-specific SIRs were calculated from the sum of the strata and an overall SIR from an aggregate of the country-specific data. The observed number of cancer cases was assumed to follow a Poisson distribution, and 95% CIs were calculated using an exact method.

Mortality: calculation of standardised mortality ratios (SMR)
Standardised mortality ratios (SMR) were calculated, by country, as the ratio between the number of deaths observed in GeNeSIS and the expected number of deaths based on reference data. The expected count was determined using gender- and age-specific mortality rates for the general population in the USA (CDC Wonder database page) and for non-US countries (WHO GHO data repository page), using the corresponding number of patient-years in GeNeSIS. An estimate of total SMR was calculated using the pooled results from the "by-country" and "regional" analyses. Exact 95% CIs were calculated for mortality rate and SMR, assuming that the observed number of deaths followed a Poisson distribution.

Efficacy
Factor associated with final height in patients with GHD: linear regression modelling
Attainment of FH was defined by at least one of the following: closed epiphyses, height velocity <2 cm/year, or last bone age ≥ 14 years in girls or ≥16 years in boys.
The population of patients meeting FH criteria were split into model and validation subpopulation.
Descriptive statistics of baseline, first year height velocity (HV) outcomes, and FH characteristics for the FH population, model population and validation population were reviewed to ensure that the model and validation population did not differ with respect to the variables being investigated.

The following combinations of model type were investigated for FH as the response variable:
- Type 1 models with baseline characteristics only as explanatory variables; including IGF (insulin-like growth factor) variables
- Type 1 models with baseline characteristics only as explanatory variables; excluding IGF variables
- Type 2 models with first year HV as an explanatory variable as well as baseline characteristics; including IGF variables
- Type 2 models with first year HV as an explanatory variable as well as baseline characteristics; excluding IGF variables

➢ Results

- **Recruitment/ Number analysed**

A total of 22,845 patients were enrolled (22,311 treated, 457 untreated, 77 unknown therapy group) from 827 sites in 30 countries.

- **Baseline data**

The proportions of patients in main diagnostic categories were GHD (62%), ISS (13%), TS (8%), SGA (6%), and SHOX-D (3%). Mean age of patients at entry into the study was 10.5 years and mean age at start of somatropin treatment was 9.6 years – the difference reflecting the population of patients treated with somatropin prior to study entry. Approximately 60% of the study population was male. Overall, the median starting somatropin dose in GeNeSIS was 0.26 mg/kg/week (ranging from 0.23 mg/kg/week for GHD to 0.32 mg/kg/week for ISS and TS), which is in accordance with the recommended starting dosage in the label. For all enrolled patients the mean follow-up time per patient was 4.2 years for somatropin-treated patients, representing approximately 90,000 person-

years of follow-up, although follow-up was slightly longer for specific populations used in the analysis of specific safety outcomes. Untreated control patients were enrolled for specific populations only, that is, those with SHOX-D and those with history of neoplastic disease; this fact coupled with the resulting limited numbers of patients means that direct treatment group comparisons are inappropriate.

- **Efficacy results**

Table 2 shows baseline height SDS, FH SDS, height gain (FH – baseline height) SDS, CA at FH and length of somatropin treatment for the main diagnostic categories. Patients were included in analysis if they met the following criteria: efficacy evaluable, GH-treated, previously treated or naïve, FH attained, baseline height SDS and FH SDS available.

Mean±SD FH SDS gain for all diagnoses combined was 1.24±1.08 SDS after 5.82±3.50 years of GH-therapy.

Table 2: Summary of baseline and final height characteristics for all diagnostic groups

Variable		All	GHD	TS	ISS	SHOX-D	SGA	CRI	other	UNK
CA (y) at FH	N	5070	3075	694	552	131	265	14	300	39
	Mean (SD)	17.26 (2.33)	17.40 (2.32)	17.11 (2.32)	17.19 (2.26)	16.39 (2.46)	16.53 (2.07)	17.33 (2.19)	17.33 (2.46)	17.19 (1.60)
HtSDS	N	5076	3080	695	552	131	265	14	300	39
	Mean (SD)	-2.42 (1.01)	-2.35 (1.04)	-2.65 (0.89)	-2.37 (0.80)	-2.36 (0.79)	-2.57 (0.86)	-2.54 (0.90)	-2.70 (1.32)	-2.30 (1.02)
FHSDS	N	5076	3080	695	552	131	265	14	300	39
	Mean (SD)	-1.18 (1.12)	-0.96 (1.12)	-1.70 (0.94)	-1.26 (0.96)	-1.50 (0.97)	-1.47 (0.84)	-1.66 (1.27)	-1.69 (1.33)	-1.54 (1.10)
FHSDS gain (FHSDS-baseline HtSDS)	N	5075	3079	695	552	131	265	14	300	39
	Mean (SD)	1.24 (1.08)	1.39 (1.14)	0.95 (0.82)	1.10 (0.98)	0.86 (0.91)	1.11 (0.96)	0.88 (0.81)	1.01 (1.10)	0.75 (0.83)
Years on GH therapy	N	4937	3009	655	547	123	262	14	292	35
	Mean (SD)	5.82 (3.50)	6.01 (3.68)	6.38 (3.34)	4.67 (2.80)	4.69 (2.61)	5.42 (2.95)	5.79 (2.82)	5.70 (3.45)	4.22 (2.54)

Abbreviations: CA= chronological age; CRI= chronic renal insufficiency; FH= final height; GH = growth hormone; GHD= growth hormone deficiency; Ht= height; ISS=idiopathic short statue; SD=standard deviation; SDS= standard deviation score; SGA=small for gestational age; SHOX-D= short stature homeobox-containing gene deficiency; TS= Turner syndrome; UNK= unknown; y=years.

When the analysis was repeated including only those patients who had at least 4 years of follow-up, the FH SDS gain increased for all diagnoses combined to 1.36±1.09 SDS after 7.14±3.39 years of GH-therapy.

Patients with short stature due to GHD had the largest proportion of patients attaining FH in the normal range (86% of all those assessed for FH), with the lowest proportion for patients with Chronic Renal Insufficiency (CRI) (64%).

- **Pharmacodynamic Evaluations**

Diabetes mellitus and abnormal glucose metabolism

During follow-up in GeNeSIS the following cases of diabetes mellitus were reported in an overall (all diagnoses) cohort of 21,448 patients from all countries with mean ± SD follow-up since start of GH-therapy of 5.0 ± 3.5 years, contributing to a total of 107,101.02 person-years of follow-up:

- 19 cases of type 1 diabetes mellitus
- 18 cases of type 2 diabetes mellitus
- 38 cases of diabetes overall (type 1, type 2 and 1 case where type was not specified)
- An additional 7 cases of diabetes were reported in patients with known underlying pathology causative for diabetes (cystic fibrosis-related diabetes, 2 cases; MELAS syndrome, 2 cases; and 1 case each of sideroblastic anaemia, post pancreatic surgery, and steroid induced diabetes). These 7 cases were not included in the case counts for the SIR calculation.

Based on expected case counts from the US general population, SIRs (95% CIs) for all countries combined were calculated as 0.92 (0.56-1.44) for type 1 diabetes, 3.77 (2.24-5.96) for type 2

diabetes), and 3.03 (2.14-4.15) for all diabetes types (including type 1 diabetes, type 2 diabetes and unknown diabetes type).
For type 2 diabetes, the statistically significantly elevated SIR observed for all diagnoses combined, appeared to be driven by patients with GHD (12 of 18 cases in the main analysis, SIR [95% CI] 3.93 [2.03 - 6.87]) and in particular those with organic GHD (8 cases, SIR [95% CI)] 9.35 [4.04 - 18.43]).

A previous analysis of abnormal glucose metabolism cases in GeNeSIS published by Child et al., including data to September 2007, had 11 confirmed cases of incident type 2 diabetes with an SIR (95% CI) for all countries combined of 6.5 (3.3 – 11.7). Of these 11 cases, risk factors for diabetes were identified in 10 patients.
With the final analysis of GeNeSIS, an additional 7 cases of type 2 diabetes were included in the main analysis. Of these 7 more recent cases, 1 patient had TS, 1 patient had a history of craniopharyngioma and obesity, and 1 patient with idiopathic GHD had a history of obesity. Two of the remaining 4 patients also had idiopathic GHD, the third patient with GHD due to pituitary hypoplasia, and the fourth patient had a diagnosis of hypogammaglobulinaemia, all with no other indicated risk factors for diabetes. Thus, of 18 patients with incident type 2 diabetes, 13 (72%) had reported risk factors for diabetes.

The results in this study report are in line with the earlier findings, meaning that most of the patients who develop type 2 diabetes during somatropin treatment had pre-existing risk factors for impairment of glucose homeostasis. Therefore, particular attention to glucose metabolism appears warranted in such patients as is recommended in the current SmPC.
Based on the currently available evidence it is endorsed that ‘abnormal glucose metabolism and type 2 diabetes mellitus’ is currently classified as important identified risk per Risk Management Plan (RMP) of Humatrope.

Primary cancer
In the cohort of GH-treated patients with no recorded previous malignancy, 14 potentially malignant primary neoplasms were identified during approximately 89,000 person-years of follow-up, with crude incidence during study estimated at 15.8 cases per 100,000 person-years. The 14 cases were from 5 countries (Canada, France, Germany, Japan, and the USA), and mean age at reported onset of cancer was 13.6 years. The SIR (95% CI) for primary cancers in GH-treated patients was 0.71 (0.39 - 1.20) for all countries combined; no individual country had a significantly elevated SIR.

Because 5 of the reported 14 cases were lymphomas, SIR calculations were repeated for lymphomas only using the corresponding lymphoma-only rates from the general population references. Four of the reported lymphoma cases were from Germany and the remaining case from France. The SIR (95% CI) for all participating countries combined was 1.93 (0.63 - 4.51) based on 2.59 expected cases from the general population; while that for the 4 German cases was 10.25 (2.79 - 26.25) based on 0.39 expected cases.

The SIRs for lymphomas were based on a small number of cases; the SIR for all countries combined was not significantly increased. Based on these results no update to the product information is needed.

Mortality
At total of 51 patient deaths were reported in patients enrolled in the GeNeSIS study; 45 were in 21,106 somatropin-treated patients who were eligible for mortality analysis. The crude mortality rate (95% CI) for all-cause mortality for somatropin-treated patients across all diagnoses was 45.86 (33.05 - 61.99)/100,000 person-years. The overall SMR for all-cause mortality was 0.61 (0.44 - 0.82). However because mean ± SD follow-up per patient was 4.3 ± 3.1 years, the SMR calculation was repeated including only patients who had ≥4 years of follow-up in GeNeSIS or who died during the study at any time (4-year population), increasing the average follow-up in study to 7.1 ± 2.6 years. When the analysis was restricted in this way the SMR for all-cause mortality for all countries was 0.81 (0.58 - 1.10).

Mortality analyses were also performed by short stature diagnosis group using country-specific general population data. Patients with GHD due to organic causes, and in particular those with history

of malignancy, had statistically significantly elevated SMR when compared to the general population registries.

Overall, no increased risk of mortality was observed; there was, however, a not unexpected increase in mortality risk for children with history of malignant neoplasia compared with children in the general population. Based on these results there is no need to update the product information.

As outcome of the referral in 2011/2012 a contraindication was included in the product information of somatropin medicinal products (including Humatrope) stating that somatropin must not be used when there is evidence of activity of a tumour and treatment should be discontinued if there is evidence of tumour growth. In addition, a warning was included that the maximum recommended daily dose should not be exceeded.

Cerebrovascular disease (CVD)
There were 3 reported TEAEs (Treatment emergent adverse event) of intracranial haemorrhage in somatropin-treated patients reported in the GeNeSIS database, three cases of stroke of unknown type and ten patients had reported ischemic cerebrovascular events during GeNeSIS.
From the total of 16 patients with reports of nontraumatic CVD in somatropin-treated patients in GeNeSIS, 11 had prior history of intracranial tumour and associated treatments.

Results from GeNeSIS did not support the findings of an increased risk for cerebrovascular disease observed in the French cohort of the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study. The last Periodic Safety Update Single Assessment (PSUSA) of somatropin (May 2016) also concluded that the currently available data do not allow to progress on any conclusions on the issue of stroke, Intracranial haemorrhage and intracranial aneurysm. These are important potential risks per RMP.

Neoplasm recurrences
There were 85 reports of recurrences in 74 of 1087 (6.8%) somatropin-treated children with ≥1 follow-up visit available and history of previous neoplasm. There were 77 cases of intracranial tumour recurrence in 67 of 823 (8.1%) patients, with recurrence of craniopharyngioma being most common (42 episodes in 37 patients), followed by recurrence of astrocytoma (11 cases) and medulloblastoma (9 episodes in 6 patients).

The proportions of relapse (recurrence/progression) before GeNeSIS and during GeNeSIS participation appeared similar in somatropin-treated and untreated patients.

Currently, there is no evidence for an increased risk of neoplasm recurrence in somatropin-treated patients. The product information already warns for the recurrence of neoplasm (brain). Furthermore, recurrence of neoplasm is classified as an important potential risk per RMP.

Second neoplasia
There were 34 reports of potential second neoplasms in 31 of 622 (5.0%) somatropin-treated survivors of childhood cancers. There were 10 reports of second neoplasms in 9 of 114 (7.9%) untreated childhood cancer survivors. Some form of radiation therapy for the primary neoplasm was reported on the serious adverse event (SAE) report and/or GeNeSIS CRF for 25 of the 31 somatropin-treated patients with second neoplasm.

These results confirm the need to monitor somatropin-treated patients with history of previous intracranial tumour and irradiation for development of second neoplasms, as is recommended in the current SmPC. Second neoplasm is included as important potential risk per RMP.

Insulin-like growth factor values
The GeNeSIS reported post baseline IGF-I SDS values in somatropin-treated patients were on average well within the normal range (-2 to +2 SDS) as evidenced by third quartile values at approximately 1.0 SDS across 4 years of somatropin treatment. The MAH stated that it appeared that somatropin doses were in general appropriate to increase to and maintain patients within normal IGF-I range.

Adverse events

At least 1 treatment emergent adverse event was reported for 30.1% of GH-treated patients with only 4.4% reported as being possibly related to somatropin by the investigator. The most prevalent TEAEs (affecting >1% of patients) were headache (2.9%), hypothyroidism – type not specified (2.8%), scoliosis (2.0%), attention deficit/hyperactivity disorder (1.8%), arthralgia (1.8%), secondary hypothyroidism (1.5%) and precocious puberty (1.3%). These numbers reflect adverse events both related and unrelated to somatropine use. The MAH noted that the most common adverse events included common childhood conditions and known potential side effects of somatropin.

The number of reported SAE in GeNeSIS was low, with at least 1 SAE reported by 567 of 22,294 (2.5%) somatropin-treated patients. There was no individual event reported by >0.15% of patients, with those with reported frequency >0.05% being pneumonia (0.11%), craniopharyngioma (0.09%), hypoglycemia (0.09%), gastroenteritis (0.08%), vomiting (0.07%), seizure (0.07%), and appendicitis (0.06%). These numbers reflect adverse events both related and unrelated to somatropine use. The MAH noted that the most common SAEs were common childhood conditions or associated with underlying disease. The MAH has concluded that no new safety signals were observed in the GeNeSIS database in patients receiving somatropin treatment.

Most of the reported adverse events (hypothyroidism, scoliosis, arthralgia) are known with the current safety profile of somatropin and are currently sufficiently covered by the SmPC and RMP. The MAH's conclusion that no new safety signals were observed is accepted based on the available data.

3. Discussion on clinical aspects

Efficacy

Paediatric data on the final height standard deviation score gain in the approved indications are: Growth hormone deficiency, -0.96 ± 1.12; Turner syndrome, -1.70 ± 0.94; short stature homebox containing gene deficiency, -1.50 ± 0.97; small for gestational age, -1.47 ± 0.84; and chronic renal insufficiency: -1.66 ± 1.27.

Safety

The incidence of type 2 diabetes during somatropin treatment remains low, with approximately 1 case for every 5,000 person-years of treatment. While somatropin product labelling recommends monitoring of glucose metabolism of patients receiving GH-therapy, this study indicates that most patients who develop type 2 diabetes during somatropin treatment have pre-existing risk factors for impairment of glucose homeostasis. Therefore, particular attention to glucose metabolism appears warranted in such patients as is recommended in the current SmPC.

Somatropin-treated paediatric patients who had no history of previous malignancy did not appear to have a higher risk for all-sites primary cancer during GeNeSIS, when compared to general population cancer registries. It should be noted that the mean duration of follow-up was only 4.2 years. Similarly there is no evidence for an increased risk of neoplasm recurrence, and in particular intracranial tumour recurrence, in somatropin-treated patients with history of such diseases. Final GeNeSIS data on second neoplasms do not offer any direct evidence to support an increased risk of second neoplasm in somatropin-treated childhood cancer survivors, who clearly have risk factors other than somatropin, for development of subsequent neoplasms. The product information already warns for the recurrence of neoplasm (brain). Furthermore, recurrence of neoplasm is classified as an important potential risk per RMP.

Two published studies from the French cohort of the SAGhE study have previously raised concerns regarding increased mortality and increased haemorrhagic CVD in somatropin-treated patients considered at low risk to mortality/morbidity (GHD, ISS, and SGA) compared to specific general population registries. In GeNeSIS, no increase in risk of mortality for children with idiopathic GHD, ISS, SGA or those without underlying serious medical problems was observed; there was, however, a not unexpected increase in mortality risk for children with history of malignant neoplasia compared with children in the general population. The 3 cases of haemorrhagic CVD, observed in GeNeSIS, were in patients with significant risk factors.

Most of the reported adverse events (hypothyroidism, scoliosis, arthralgia) are known with the current safety profile of somatropin and are currently sufficiently covered by the SmPC and RMP. No new safety signals were observed in the GeNeSIS database in patients receiving somatropin treatment.
The safety outcomes of the study, with almost 20 years of real life available data at this stage – should also be reflected in the SmPC (e.g. section 5.1), taken into account the limitations of the study.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The incidence of type 2 diabetes in GeNeSIS is significantly higher than that observed in the contemporary general population data. However, most of the patients who develop type 2 diabetes during somatropin treatment have pre-existing risk factors for impairment of glucose homeostasis. Therefore, particular attention to glucose metabolism appears warranted in such patients as is recommended in the current SmPC.

Somatropin-treated paediatric patients who had no history of previous malignancy did not appear to have a higher risk for all-sites primary cancer, when compared to general population cancer registries. It should be noted that the mean duration of follow-up was only 4.2 years. Similarly, there is no evidence for an increased risk of neoplasm recurrence in somatropin-treated patients with history of such diseases. This is consistent with other studies and the current product labelling. Please note that second neoplasm in somatropin-treated childhood cancer survivors is an important potential risk per RMP.

Overall, no increased risk of mortality was observed; there was, however, a not unexpected increase in mortality risk for children with history of malignant neoplasia compared with children in the general population. Results from GeNeSIS did not support the findings of an increased risk for cerebrovascular disease observed in the French cohort of the SAGhE study.

No new safety signals were observed in the GeNeSIS database in patients receiving somatropin treatment. The current safety profile is sufficiently covered in the product information and RMP.

The efficacy data on the final height standard deviation score gain should be included in SmPC. The safety outcomes of this final study report should also be reflected in the product information.

Overall the final results regarding efficacy and safety of the post-authorisation safety study based on approximately 90,000 patient-years of exposure and 4,2 years of mean follow up are reassuring and confirm the currently positive benefit-risk balance of Humatrope (somatropin) in the treatment of its approved indications.

The MAH has adequately addressed the questions raised by the Medicine Evaluation Board. Based on the review of the submitted data, it has been concluded that the SmPCs of Humatrope should be updated to include results of the GeNeSIS study. Efficacy data on the final height standard deviation score gain should be included as well as safety outcomes of the final study report. The wording of section 5.1 of the SmPC as proposed by the MAH is considered acceptable.

Following the finalisation of this procedure, the MAH should submit variations in all European countries where Humatrope is currently registered.

It has been considered that the overall benefit/risk ratio of Humatrope in the paediatric population remains unchanged.

➢ Recommendation

A variation to be requested from the MAH within three months after finalisation of this procedure.

SmPC wording in section 5.1:

Paediatrics

An open-label, multicentre, observational study GeNeSIS (Genetics and Neuroendocrinology of Short Stature International Study) was established as a post-authorization safety surveillance programme. Paediatric data on the final height standard deviation score gain in the approved indications are: Growth hormone deficiency, 1.39 ± 1.14; Turner syndrome, 0.95 ± 0.82; short stature homeobox containing gene deficiency (SHOX-D), 0.86 ± 0.91; small for gestational age (SGA), 1.11 ± 0.96 and chronic renal insufficiency (CRI), 0.88 ± 0.81 after 6.0 ± 3.7, 6.4 ± 3.3, 4.7 ± 2.6, 5.4 ± 3.0, and 5.8 ± 2.8 years of somatropin treatment, respectively.

Results from a long-term observational study (GeNeSIS) of paediatric somatropin treatment included data from 22,311 somatropin-treated patients (63.0% growth hormone deficiency, 12.7% idiopathic short stature, 8.4% Turner syndrome, 5.7% children born small for gestational age, 2.6% SHOX deficiency, 0.4% chronic renal insufficiency, 5.5% other, and 1.7% unknown) and were consistent with the known safety profile of somatropin. Key safety objectives of incidence of type 2 diabetes, de novo cancers and mortality were assessed by comparison to contemporary general population registry data. Eighteen of the 21,448 somatropin-treated patients eligible for analysis developed type 2 diabetes mellitus in the study; however, 13 out of the 18 patients had reported pre-existing diabetes risk factors. The standardised incidence ratio (95% CI for type 2 diabetes in somatropin-treated children was significantly elevated [3.77 (2.24 to 5.96)], but the incidence at 16.8 cases per 100,000 person-years of exposure is rare. The standardised incidence ratio (95% CI) for all-sites primary cancers in patients with no previous cancer history was 0.71 (0.39 to 1.20), based on 14 cases. There were 45 reported deaths in somatropin-treated patients.

The standardised mortality ratio (95% CI), based on 42 deaths in patients who had follow-up during study, was 0.6 (0.4 to 0.8) for all-cause mortality for all short stature diagnoses combined; only the diagnostic subgroups of patients with a history of organic growth hormone deficiency, and in particular due to previous malignancy, had a significantly elevated standardised mortality ratio.