Australian Public Assessment Report
for
Somatropin

Proprietary Product Name: Genotropin

Submission No: PM-2008-2730-5

Sponsor: Pfizer Australia

March 2010

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	Product information change, requiring the evaluation of clinical, non-clinical or bioequivalence data
Decision:	Amend the dosage and administration section - Approved; Remove a Contraindication – Withdrawn by sponsor
Date of Decision:	19 December 2009
Active ingredient(s):	Somatropin
Product Name(s):	Genotropin
Sponsor's Name and Address:	Pfizer Australia 38 - 42 Wharf Road West Ryde NSW 2114
Dose form(s):	Powder for injection
Strength(s):	Genotropin: 5 mg and 12 mg Genotropin MiniQuick: 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 mg
Container(s):	Two-compartment glass ampoule
Pack size(s):	Genotropin: pack of 1 and 5 Genotropin MiniQuick: pack of 7
Approved Therapeutic use:	• Short stature due to decreased or failed secretion of pituitary growth hormone. • Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL. • Growth disturbances associated with gonadal dysgenesis (Turner syndrome). • Improvement of body composition and treatment of short stature associated with Prader-Willi syndrome (PWS) in paediatric patients. • For treatment of growth disturbance in children with chronic renal insufficiency whose height is on or less than twenty-fifth percentile and whose growth velocity is on or less than twenty-fifth percentile for bone age. Chronic renal insufficiency is defined as glomerular filtration rate of less than 50 mL/min/1.73 m$_2$.
Route(s) of administration:	Subcutaneous injection
Dosage:	Dosage requirements differ with different indications

Product Background

Genotropin is recombinant human growth hormone (somatropin) and is commercially available as 5mg and 12mg powder for injection with diluent (with preservative) and 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0mg powder for injection with preserved diluent in single-use syringes.

After reconstitution, Genotropin (5mg and 12mg), two-compartment cartridges contains somatropin (5mg or 12mg), glycine, mannitol, sodium phosphate-monobasic, sodium phosphate-dibasic anhydrous, meta-cresol and Water for Injections.

After reconstitution, Genotropin Miniquick, two-compartment cartridges contains somatropin (0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 or 2.0mg), glycine, mannitol, sodium phosphate-monobasic, sodium phosphate-dibasic anhydrous and Water for Injections.

Genotropin is administered by subcutaneous injection and the injection site should be varied in an attempt to prevent lipoatrophy.

The sponsor has not applied to change the currently approved indications (previous page).

The current application is to vary the conditions for registration of Genotropin with respect to the following:-

- amend the dosage and administration section of the product information (PI0 to express the dose in children as a weekly dose instead of a daily dose, and include instructions for the use of the Pfizer administration device (Genotropin Pen) with Genotropin cartridges.

- remove the Contraindication of somatropin in the treatment of patients with Prader-Willi syndrome (PWS) who are severely obese or have severe respiratory impairment, and add a statement under "Adverse Reactions" on the post-marketing experience of sudden death in patients with PWS.

With respect to the first variation, the dosing schedule has varied over the years but the reversion to including a weekly total requires an application. This is a minor matter that would not require referral to the Australian Drug Evaluation Committee (ADEC) nor would it result in the generation of an AusPAR.

The use for the indication of Prader-Willi Syndrome was based on approval as an Orphan Drug. In line with TGA policy, the FDA's evaluation was used as the primary evaluation report and the application was not referred to AEDC. Registration was approved on 20 March 2001. The Contraindication was inserted, via a safety related notification, by the current sponsor's corporate predecessors on 20 May 2003. Because the Delegate considered the request for deletion of the Contraindication to be unacceptable the application was referred to ADEC and therefore an AusPAR has been generated.

Prader-Willi Syndrome (PWS) is a complex genetic, multisystem disorder, characterised by hypothalamic dysfunction. The syndrome course changes with age, initially manifesting as severe neonatal hypotonia, feeding difficulty in infancy and dysregulation of temperature in young children and hyperphagia, massive obesity, diabetes mellitus (DM), respiratory failure and cor pulmonale in adolescents and adults. The diagnostic criteria (based on clinical findings) are used to identify patients for genetic testing more than to establish diagnosis of disease. Approximately 70% carry a deletion of paternally derived chromosome 15 (q11-q13); approx. 25% have maternal uniparental disomy of chromosome 15 (2 maternal and no paternal chromosome 15). PWS is associated with relatively high rates of morbidity due to hypotonia and obesity-related illnesses. Patients with PWS are recognised to have a tendency of sudden death; respiratory failure and respiratory infections have been suggested as potential causes of death in infants and children; obesity-related complications such as non-insulin dependent diabetes mellitus (NIDDM), hypertension, respiratory disorders and cardio-respiratory failure are potential causes of death in adults.

Burman has reviewed the results from a number of studies which suggest possible mechanisms of action of growth hormone (GH) in PWS:[1]

(1) Peak GH levels at stimulation tests are similar to classical GH deficiency in 40-100% of PWS patients,
(2) Progressive growth retardation occurs in most children with PWS and GH treatment has similar effects on linear growth in PWS as in children with classical GH deficiency; and
(3) GH has beneficial effects on body composition, lipids, carbohydrates and bone metabolism.

Regulatory Status

The product received initial ARTG Registration in 1991 and a number of products are registered.

The currently approved PI for Genotropin in USA has the weekly dose. However, the Contraindication in Prader-Willi Syndrome patients who are severely obese or who have severe respiratory impairment has been retained in the US PI.

The Contraindication has been removed from the PI approved in European Union (EU) countries.

II. Quality Findings

Quality Summary and Conclusions

There is no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There is no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical Findings

Introduction

The current application is to vary the conditions for registration of Genotropin with respect to the following:-

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A number of Benefit-Risk assessment reports on PWS issues have been submitted to the Reference Member State (RMS) and Country Member States (CMS) of the EU and copies of these reports have been provided to support the current application. The reports include an update of the post-marketing experience on mortality in PWS patients and reviews of the published literature on morbidity and mortality in PWS patients. Updates to the data from an epidemiology study are also provided. A number of literature references on PWS were provided, although a systematic literature review was not conducted.

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[1] Burman, PM, Reports from literature. Published clinical data on the use of growth hormone in Prader-Willi syndrome. A literature review through June 1999, P. Upjohn, Editor.

Review of Proposed Product Information Changes

Review of Data on Dosing

The currently approved Australian PI for Genotropin has the following dosing and comments regarding the new proposed weekly dosing regimen have been provided in *italic font*:-

Children with growth hormone deficiency The diagnosis of growth hormone deficiency should be verified before the preparation is administered. This requires a thorough investigation of the pituitary function, including proper provocation tests. The dosage is individual and gradually titrated, but generally an initial dose of **0.025 to 0.035 mg/kg bodyweight/day** is recommended. *The new dosing advice is 0.175 to 0.245mg/kg body weight per week.*

Turner syndrome A dose of **0.045 to 0.050 mg/kg bodyweight/day** is recommended. *The new dosing advice is 0.3 to 0.35mg/kg body weight per week.*

Prader-Willi syndrome The diagnosis of PWS should be confirmed by appropriate genetic testing. Generally a dose of **0.035 to 0.050 mg/kg bodyweight/day** is recommended. *The new dosing advice is 0.245 to 0.35mg/kg body weight per week.*

Chronic renal insufficiency A dose of **0.045 to 0.050 mg/kg bodyweight/day** is recommended. *The new dosing advice is 0.3 to 0.35mg/kg body weight per week.*

Adults with growth hormone deficiency The recommended dosage at the start of therapy is **0.04 mg/kg/week** divided into seven daily subcutaneous injections. This dose should be gradually increased according to individual patient requirements to a **maximum of 0.08 mg/kg/week.** Dose titration is based on the development of side effects and determination of serum levels of insulin-like growth factor (IGF-1). Dose requirements may decline with increasing age. *The dosing for this indication has not been changed as it was a weekly dose in the earlier approved PI.*

Bioequivalence has not been demonstrated between Genotropin 5 mg or Genotropin 12 mg administered in the Genotropin Pen injection device and Genotropin MiniQuick.

It is recommended that regular monitoring of growth rate and measurement of biochemical markers, such as IGF-1 levels, be undertaken to ensure adequate delivery of growth hormone and compliance with therapy.

Conclusion

The evaluators confirmed that the mg dose has not been altered while changing the presentation in the PI from daily to weekly dose (given over 6-7 subcutaneous injections).

Review of Additional Data in PWS Patients

Clinical expert report (August, 2005)

Within the context of the Genotropin Mutual Recognition Renewal Procedure in the EU, one of the CMSs requested Pfizer to submit a reassessment of the risk-benefit ratio in PWS in the light of data on fatal outcomes submitted to the CMS in February 2005. PWS is a rare syndrome (estimated birth incidence of PWS range from 3 to 7 per 100,000 live births) and it is difficult to conduct conventional large scale clinical trials. This report included epidemiological assessment and post marketing experience.

Epidemiological assessment

In this report dated August 2005, 7 individual case reports, 4 case series and one population-based study provided data on mortality in PWS patients. No study directly evaluated and compared mortality in PWS patients receiving GH treatment with that in patients not receiving GH treatment. Information on mortality in GH-treated patients (from individual case reports) showed similar

contributing factors for mortality to those observed among patients not treated with GH (from 3 case series).

In a multinational collaborative study, descriptive information on 27 fatal cases in PWS patients was reported (13 deaths in patients aged <5years and 14 deaths in those aged >9 years). None of the unexpected deaths in this series were treated with GH and they experienced the same causes of death as the GH-treated fatal cases in the individual case reports.

A retrospective review of data from 2 Japanese societies reported 13 cases of sudden unexpected deaths out of a total of 494 PWS patients (265 males, 229 females). Seven of these deaths were in infants aged <3 years and obesity was not reported in any of these cases; 4 of the other 6 deaths in patients aged 14 to 48years reported massive obesity, diabetes mellitus, respiratory problems and/or renal/cardiac failure as contributory factors (2 unexpected deaths happened while bathing). A population-based study conducted in a UK region of approximately 5 million people made an indirect estimate of mortality of 3% in PWS patients based on 96 cases (age ranging from 0 to 47 years). However, the proportion of GH-treated patients was not reported in the above studies and original references were not available for review. The epidemiological assessment presented above did not provide any definitive evidence of any relationship between the incidence of deaths in PWS patients and severe obesity or severe respiratory impairment. However, it is important to stress again that none of the studies directly compared mortality in PWS patients receiving GH treatment with that in those not receiving GH treatment.

Post marketing experience of mortality in PWS

Pfizer's safety database was reviewed for PWS adverse event cases reported up to 15 June 2005. Approximately 15% of all PWS cases identified had a fatal outcome. The majority of the fatal cases (74%) involved male patients and most (90%) involved patients < 16 years of age. Approximately 40% of the fatalities appear to be related to respiratory disorders, the majority of which were present prior to the start of somatropin therapy. Almost all of the remaining cases did not report a specific cause of death, however about 50% experienced a respiratory event at or near the time of death and/or had a history of respiratory disorder prior to starting somatropin therapy. Just over half of the patients had been on somatropin therapy for 1 to 6 months at the time of their death, and about a third had been taking somatropin for > 1 year. About 11% of the fatalities occurred within the first month of therapy, and about 5% from 7 to 11 months of therapy. Approximately 67% of the patients who died within 6 months of starting somatropin therapy appear to have died as a result of their underlying respiratory disorder or experienced respiratory events at the time of their death.

Postmarketing experience (July 2006)

As of July 2006, the total number of PWS patients in the Pfizer surveillance safety database was 1212 (2436 patient years). No new deaths were reported since the expert report of August 2005 (see above).

Postmarketing experience (July, 2007)

Update on mortality in PWS patients

Since the last report in August 2005 and as of May 2007, a few additional deaths were identified through the Pfizer safety surveillance database. Overall 13% of all PWS cases reported up to 31 May 2007 had a fatal outcome. The majority of deaths reported were reported to involve patients aged <15 years of age (93%) or males (69%). The information for several patients included in the August 2005 report was revised and updated in the 2007 report due to either receipt of follow-up information or correction of data upon re-examination of the case. Overall, almost 40% of fatal cases reported a cause of death that was related to the respiratory system (most had existing respiratory disorders prior to starting somatropin therapy). Of the cases that did not report a cause of death, 75% experienced a respiratory event at or near time of death (about 40% of these cases also

had pre-existing respiratory disorders prior to start of somatropin therapy). Of the remaining cases, cause of death was drowning, heart dilatation due to unspecified heart defect, gastric perforation and traffic accident.

The majority of PWS patients that received somatropin treatment were between 1 to 10 years of age (median age of the 1135 somatropin-treated patients with PWS enrolled in the Pfizer International Growth database as of Jan, 2006 was 6.4 years). Overall, 85% of the reported deaths occurred in patients <15 years of age.

Table 1: Fatal PWS Cases from Post-marketing/Pharmacovigilance data

Characteristic		Number of Cases
Gender	Male	18 (69.2%)
	Female	7 (26.9%)
	Unknown	1 (3.8%)
Age (years) range: 0.7-48 Mean = 10.5 (n=26)	≤ 15	24 (92.3%)
	31-50	2 (7.7%)
Source	Clinical Study	10 (38.5%)
	Health Authority	3 (11.5%)
	Literature	8 (30.8%)
	Spontaneous	5 (19.2%)

Overall, the most common duration of somatropin treatment was 1 to 6 months (43%) and >1 year (43%); these were the most frequent durations of somatropin treatment in patients <5 years and 10-15 years of age, respectively.

The majority of the deaths cumulatively through 31 May 2007 were in males and patients aged <15 years of age. Causality was reported in 46% of these cases; all but 1 of the reported clinical study reports were assessed as not related, and 1 clinical study report was assessed as related (intercurrent convulsion disorder around time of death in a patient treated with somatropin for >1year). A few spontaneous reports were assessed as not related to somatropin treatment. Half of the fatal cases reported respiratory disorders prior to start of somatropin treatment and also half involved patients taking somatropin for ≤ 6 months at the time of their deaths (62% died of underlying respiratory causes or experienced respiratory events at or around time of their death). The data provided was inadequate as cause of death was not provided for 54% of the fatal cases.

Postmarketing experience (July, 2008)

Update on mortality in PWS patients

Updated postmarketing experience on mortality in PWS

Since the last report in June 2007 and as of May 2008, no additional deaths were identified through the Pfizer safety surveillance database. Overall, cases that reported an indication of PWS represented 2% of all somatropin cases received into the safety database up to 31 May 2008. Of the PWS cases, 11% reported a fatal outcome.

Literature update on breathing disorders in PWS patients

Two reports from investigator-initiated, Pfizer-supported studies provided information on the effect of somatropin treatment on the underlying respiratory disorders in patients with PWS.

Festen et al evaluated the occurrence of sleep related breathing disorders (SRBDs) in 53 children with PWS, 35 of whom were re-evaluated after 6 months of GH treatment.[2] Polysomnography (PSG)

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[2] Festen, Wevers M, et al. Mental and motor development before and during growth hormone treatment in infants and toddlers with PWS. Clin Endocrinol 2008; 68 (6): 919-925.

revealed that baseline median apnoea hypopnoea index (AHI-defined as the mean number of periods of apnea and hypopnea per hour of sleep) for the 53 patients was 5.1 (range 2.8 to 8.7), which was significantly above the normal range of 0 to 1. Of these, 2.8 per hour (1.5 to 5.4) were identified as central apnoeas, 0.0 per hour (0 to 0.3) as obstructive apnoeas and 0.9 (0 to 2.7) as hypopnoeas. There was no correlation between body mass index (BMI), standard deviation score (SDS) and AHI for the group as a whole, but obstructive apnea was more likely in obese patients (4 of 8 obese children had obstructive apnea). In the 35 subjects followed during GH treatment, there was a slight non-significant reduction in median AHI from 4.8 (2.6 to 7.9) to 4.0 (2.7 to 6.2) (see below).

Clinical and respiratory parameters of GH-treated group

	Before start of GH		After 6 months of GH		P value
	Median	iqr	Median	iqr	
No.	35		35		
Gender	20 boys/15 girls		20 boys/15 girls		
Age (yr)	6.0	2.3–8.6	6.8	3.1–9.9	
BMI (kg/m²)	17.1	15.9–19.2	17.6	15.7–18.9	0.36
BMI (SDS)	0.6	−0.1 to 1.5	0.8	−0.1 to 1.2	0.19
AHI	4.8	2.6–7.9	4.0	2.7–6.2	0.36
Central apnea index	2.9	1.5–5.2	2.2	0.8–4.1	0.15
Obstructive apnea index	0.0	0.0–0.3	0.0	0.0–0.2	0.73
Hypopnea index	0.7	0–1.9	1.0	0.7–2.0	0.26
Longest apnea (sec)	15.0	13.0–25.0	17.0	14.0–23.3	0.92

Data are expressed as median (iqr). Respiratory parameters did not change significantly during GH treatment (Wilcoxon signed rank test).

Tonsillectomy and adenoidectomy was performed in 5 of these subjects because tonsillar and/ or adenoidal hypertrophy developed during the course of follow-up. One 3-year old patient died unexpectedly, 13 months after starting GH treatment; PSG revealed an AHI of 1.7 per hour (100% central apnea) before starting GH treatment and an AHI of 1.4 per hour (67% central, 33% hypopnea), 6 months after starting GH treatment. He had a mild upper respiratory infection (but otherwise in good health) when seen by paediatrician, the day before his death. In this study, the incidence of obstructive apnea was small both before and during GH treatment. The median AHI, especially the incidence of obstructive apnea appears to increase during URTI compared to good health (see table below).

TABLE 2 Respiratory parameters during health and URTI (n = 4)

	Health		URTI		P value
	Median	iqr	Median	iqr	
AHI	5.7	3.1–9.5	36.5	15.1–39.5	0.07
Central apnea index	2.7	1.5–6.5	6.4	1.9–6.5	0.27
Obstructive apnea index	0.0	0.0–2.5	8.9	2.4–21.0	0.07
Hypopnea index	1.1	0.0–3.5	7.2	3.6–20.3	0.14
Longest apnea (sec)	34.5	18.5–33.5	35.5	27.3–49.8	0.27

Data are expressed as median (iqr). Respiratory parameters were as measured by PSG in health and during an episode of URTI. P values are depicted for the statistical analyzes (Wilcoxon signed rank test) between measurements during health and URTI.

Results from this study showed that a normal PSG does not exclude the possibility of unexpected death during mild upper respiratory tract infection (URTI). Although there was a slight non-significant reduction in AHI following 6 months of GH treatment, results do not confirm lack of a detrimental effect of GH on SRBDs, especially due to likelihood of adenoid and tonsillar hypertrophy following GH treatment.

Another smaller study (Salvatoni A et al) evaluated the occurrence of SRBD in 12 patients with PWS before and after 6 weeks of GH treatment.[3] Each patient underwent PSG and ear nose and throat (ENT) video endoscopy before and after 6 weeks of GH treatment (0.03mg/kg/day). At baseline, all 12 patients showed central and/ or obstructive sleep disordered breathing and all

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[3] Salvatoni A, et al. Short-term effect of rhGH treatment of children with PWS on respiratory function: a polysomnographic and ENT endoscopic study. Presented at the 46th annual meeting of the European Society for Paediatric Endocrinology (ESPE), June 30, 2007.

underwent local and general steroid treatment until normalisation of the obstructive apnea index (OAI). No significant changes were observed in PSG indexes following 6 weeks of GH treatment; however, OAI increased in 42% (5/12), decreased in 25% (3/12) and did not change in 33% (4/12) of the patients. There was no correlation between body fat, IGF, insulin and PSG during GH treatment. Although video endoscopic evaluation showed no increase of tonsillar and adenoid size after GH treatment, it is important to note that OAI did show an increase in 42% of patients. However, this study failed to provide any conclusive evidence due to small sample size and shorter duration of GH treatment in this study.

Literature updates on morbidity and mortality in PWS

An epidemiological study by the Italian National Survey for PWS (Grugni et al) followed 425 patients with PWS between January 1986 and June 2006.[4] These included 209 males and 216 females between the ages of 0.4 to 46.7years, of whom 407 were still alive as of 30 June 2006. About half of the patients (212) had received GH treatment and 141 were on active treatment at the time of the study. Of the 233 patients aged <18 years (130 males and 103 females), 116 were on GH treatment, 28 had previously received GH and 89 had never received GH treatment. In the 192 adults, only 25 were on GH treatment and 43 had stopped GH therapy (35 adults had received GH during childhood and 17 were treated both before and after 18 years of age). The duration of GH treatment ranged between 2 and 169 months and the median dose in children and adolescents was 0.196mg/kg per week (0.11 to 0.43mg/kg per week), whereas in adults, it was 0.044mg/kg per week (0.011 to 0.079mg/kg per week). There were 18 deaths over the 20-year period (6 and 12 deaths in patients < and >18 years of age, respectively). In the younger group, 3 of the 6 patients died while receiving GH treatment, whereas only 1 of 12 patients in the older group had undergone GH treatment during childhood but had stopped 8 years prior to his death. Overall, the frequency of death during GH treatment was 1.41% (3/212) whereas it was 7.04% (15/213) in patients not on GH treatment, although very small numbers make interpretation difficult. In patients < 18 years of age, the frequency of death was 2.08% (3/144) and 3.37% (3/89) in GH-treated and untreated patients, respectively.

Einfeld et al showed that patients with PWS had 6.07 (95% confidence intervals (CI): 1.87, 19.73) times the risk (hazard) of death of the control subjects; 6 of 37 patients with PWS and 27 of 547 control subjects (aged 4-18 years) died, resulting in a rate of death per 1000 person years of 16.4 and 4.3, respectively.[5] However, none of the children in this study received GH treatment and this study did not contribute any data towards risk-benefit assessment of GH treatment in PWS. Another review of deaths in children with PWS was based on a literature search (bibliographic databases, toxicology and pharmacovigilance databases and electronic archives of French medical reviews) for reports of deaths among PWS patients aged ≤ 20 years during the period 1980-2007 (Tauber et al).[6] The review identified 64 deaths (42 males, 22 females) in children and adolescents with PWS ranging in age from the neonatal period to 19 years (median of 3 years). Of these 64 patients, only 28 received GH Treatment.

Respiratory disorders were the most common cause of death in both GH-treated and untreated patients (61%). In the GH-treated patients, a majority of the deaths occurred early in the course of GH treatment; 21 of the 28 deaths occurred during the first 9 months following initiation of GH treatment. Of the 25 children < 3years of age at the time of death, only 3 received GH treatment and

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[4] Grugni G, et al. The Italian National Survey for PWS:an epidemiology study. Am J Med Genet A 2008; 146: 861-72.

[5] Einfeld SL, et al. Mortality in PWS. Am J Ment Retard 2006; 111: 193-8.

[6] Tauber M, et al. Review of 64 cases of death in children with PWS. Am J Med Genet A 2008; 146: 881-7.

22 were untreated. However, in patients aged >3 years, the relative number of GH-treated and untreated patients at the time of death was similar (28% and 29%, respectively). Results from this review suggested that most of the deaths occurred during the first 9 months of GH treatment and may be potentially related to GH-mediated growth of tonsillar and other lymphoid tissues in the oropharynx and/ or increased respiratory needs secondary to increased caloric expenditure.

Another study (Festen, de Lind van Wijngaarden et al) evaluated adrenal function in 25 paediatric patients with PWS to assess increased risk of central adrenal insufficiency (CAI), a known cause of sudden death in children.[7] Results showed that 15 of the 25 patients (60%) with PWS had an insufficient rise in adrenocorticotropic hormone (ACTH) following metapyrone testing, confirming a diagnosis of CAI. However, patients with CAI had lower 11-deoxycortisol levels than those without CAI, but had normal diurnal cortisol profiles, suggesting that CAI occurred only during stressful conditions. Although this study was small, it seemed to suggest that presence of CAI in patients with PWS may predispose them to unrecognised adrenal crisis and sudden death during stress, such as that associated with URTI.

Literature update on safety and efficacy of Genotropin in PWS

The effects of earlier GH therapy on anthropometric measurements, body composition and psychomotor development were evaluated in 25 infants and toddlers with PWS (Myers et al).[8] The 25 patients aged 4 to 37 months were randomised to 2 years of GH therapy ($1mg/m^2$/day) or 1 year of observation without GH therapy followed by GH treatment ($1.5mg/m^2$/day) for 1 year only. GH-treated PWS patients demonstrated normalisation of length/ height standard deviation scores (SDS), faster head growth, increased lean body mass accrual and decreased body fat (p<0.005 for all parameters), as well as improved language (p<0.05) and cognitive (p=0.02) quotient Z-scores compared with similarly aged untreated PWS patients after 1 year into the study (see table below).

TABLE Anthropometric and Body Composition Data in GH-Treated and Untreated (Control) Prader–Willi Syndrome (PWS) Subjects

	GH-treated PWS subjects			Untreated (control) PWS subjects	
	Baseline	1 year	2 years	Baseline	1 year
Length/height SDS	−1.6 ± 1.2	−0.2 ± 1.5*	0.6 ± 1.2	−1.3 ± 1.1	−1.5 ± 0.7
Head circumference SDS	−0.9 ± 0.8	−0.1 ± 0.9**	0.4 ± 1.2	−0.5 ± 0.7	−0.2 ± 0.7
Body fat, %	28 ± 7	23 ± 9*	27 ± 10	29 ± 12	33 ± 8
Lean mass, kg	5.8 ± 1.9	9.8 ± 2.0*	12.4 ± 1.9	6.9 ± 2.0	8.5 ± 1.9
Bone mineral density, g/cm²	0.60 ± 0.08	0.67 ± 0.05	0.73 ± 0.04	0.64 ± 0.09	0.69 ± 0.06

*P < 0.005.
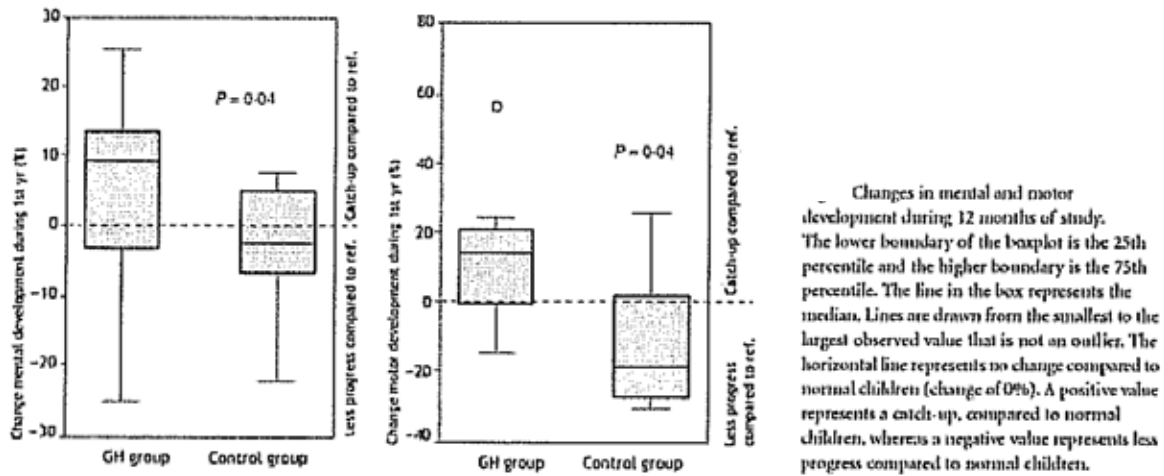**P < 0.01 compared with 12-month changes in the PWS control group.

The evaluators noted that there was no systematic assessment of sleep related breathing disorders and pulmonary function in this study.

Festen et al (2008) also analysed mental and motor development in 42 infants and toddlers.[2] Baseline psychomotor development was assessed using the Bayley Scales of Infant development II (BSD II) and results compared with reference data derived from healthy infants and toddlers of comparable age. There were no significant differences between GH-treated and control patients in terms of height, BMI, body fat, head circumference or IGF. Although, patients treated with Genotropin appeared to show significant improvement in mental development (9.3%) and motor development (11.2%) compared to values in untreated controls (-2.9% and -18.5%, respectively,

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[7] Festen DA, de Lind van Wijngaarden R, et al. Randomised controlled growth hormone trial: Effects on anthropometry, body composition and body proportions in a large group of children with PWS. Clin Endocrinol (Oxf) 2008 Mar18 (ahead of print).

[8] Myers Se, et al. Two years of growth hormone therapy in young children with PWS: Physical and neurodevelopmental benefits. Am J Med Genet A 2007; 143 (5): 443-8.

p=0.04), these results should be interpreted with caution due to wide confidence intervals (see below).

Changes in mental and motor development during 12 months of study. The lower boundary of the boxplot is the 25th percentile and the higher boundary is the 75th percentile. The line in the box represents the median. Lines are drawn from the smallest to the largest observed value that is not an outlier. The horizontal line represents no change compared to normal children (change of 0%). A positive value represents a catch-up, compared to normal children, whereas a negative value represents less progress compared to normal children.

Another randomised, controlled trial evaluated the safety and efficacy of Genotropin ($1mg/m^2$/day) treatment in 91 pre-pubertal (aged between 3 and 14 years) patients with genetically confirmed PWS. Infants and toddlers below 3.5 years of age (n=42) were stratified for age and randomised to treatment with Genotropin (n=20) or to an untreated control group (n=22) for 1 year. Children over 3.5 years old were stratified by BMI and randomised to treatment with Genotropin (n=25) or untreated control group (n=22) for 2 years. Patients <3.5 years old, who were originally in the control group during first year of study subsequently received Genotropin therapy during the second year. Infants and toddlers treated with Genotropin had a significantly greater increase in median height SDS after 1 year compared with control group (-1.0 SDS vs -1.8SDS, p<0.001) and after 2 years all treated patients had a height above -2SDS. A similar increase was observed in median head circumference. Patients over 3.5 years of age also showed similar improvements in height and head circumference with Genotropin treatment. Changes in body composition were only evaluated in patients >3.5 years and showed lower percent fat mass and increased lean body mass in treated patients compared to untreated controls.

Based on available data, Stafler and Wallis (2008) provided a risk-benefit analysis of GH in the treatment of patients with PWS.[9] The authors have reviewed the benefits of GH treatment in PWS, including GH-mediated improvements in body composition, growth, psychosocial development and its potential risks, including the potential increase in size of adenoids/ tonsils, enhanced energy expenditure and normalisation of hydration status (leading to volume overload and compounding pre-existing impaired gas exchange). The authors have also suggested a protocol to reduce the risks associated with GH treatment in PWS, especially during the early period after initiation of GH therapy. The protocol suggested by Stafler and Wallis appears to have been suggested from data reviewed by them, but as the data was not available for review to the TGA evaluators, it is not possible to comment on suitability of the protocol

Clinical Summary and Conclusions

The sponsor claims that the cases of deaths in PWS patients do not warrant the specific Contraindication due to heterogeneity in the cases. Based on data provided in this submission, it is difficult to arrive at any definite conclusions regarding association between GH treatment and the deaths reported in PWS patients. On the other hand, GH treatment may provide benefits if due

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[9] Staffler P, Wallis C. Prader-Willi syndrome: who can have growth hormone? Arch Dis Child 2008; 93: 341-5.

vigilance is exercised and a strict protocol is followed regarding initiation and maintenance of GH treatment in children with PWS

Recommendation

The TGA evaluators recommended that the dosing advice can be changed to weekly dose instead of the daily dose. The Contraindication of *Prader-Willi Syndrome patients who are severely obese or who have severe respiratory impairment* may be removed, but this would be subject to incorporation of changes in the proposed Australian PI (especially precautions before initiating GH therapy in PWS) suggested by the evaluators. However, if the sponsor is not willing to accept suggested changes to the proposed PI, then the more conservative option of retaining the Contraindication (in the PWS patients at risk who are severely obese, have history of upper airway obstruction or sleep apnea, or have known respiratory impairment) is recommended.

V. Pharmacovigilance Findings

There is no requirement for a pharmacovigilance evaluation in an application of this type.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There is no requirement for a quality evaluation in an application of this type.

Nonclinical

There is no requirement for a nonclinical evaluation in an application of this type.

Clinical

Dosing Regimen

The TGA evaluators confirmed that the mg dose has not been altered while changing the presentation in the product information document (PI) from daily to weekly dose (given over 6-7 subcutaneous injections).

Safety

The TGA evaluators described the features and morbidity associated with PWS. "PWS is associated with relatively high rates of morbidity due to hypotonia and obesity-related illnesses. Patients with PWS are recognised to have a tendency of sudden death; respiratory failure and respiratory infections have been suggested as potential causes of death in infants and children; obesity-related complications such as NIDDM, hypertension, respiratory disorders and cardio-respiratory failure are potential causes of death in adults."

The information derives from a review conducted by Pfizer for a CMS regulatory agency and a related epidemiological study, a review conducted in Japan, a published version of an Italian epidemiological study, Pfizer's own database (KIGS) and other literature.

The epidemiological review that was conducted for the CMS, "…The epidemiological assessment presented above did not provide any definitive evidence of any relationship between the incidence of deaths in PWS patients and severe obesity or severe respiratory impairment. However, it is important to stress again that none of the studies [including the Japanese study] directly compared mortality in PWS patients receiving GH treatment with that in those not receiving GH treatment."

The evaluators conclude that the majority of the deaths cumulatively up to 31 May 2007 were in males and patients aged <15 years of age. Causality was reported in 46% of these cases; all but 1 of the reported clinical study reports were assessed as not related, and 1 clinical study report was assessed as related (intercurrent convulsion disorder around time of death in a patients treated with somatropin for >1 year) and a few spontaneous reports were assessed as not related to somatropin

treatment. Half of the fatal cases reported respiratory disorders prior to start of somatropin treatment and also half involved patients taking somatropin for ≤6 months at the time of their deaths (62% died of underlying respiratory causes or experienced respiratory events at or around time of their death). The data provided was inadequate as cause of death was not provided for 54% of the fatal cases.

There are also suggestions of some pathophysiological features of children with PWS that might predispose them to sudden death, for example in the event of URTI. De Lind va Wijngaarden et al. suggest that children with PWS may have central adrenal insufficiency;[7] a Pfizer supported study (Festen et al) suggested that six months of somatropin treatment was associated with a non-significant reduction in the number of episodes of sleep related breathing disorders in 35 children with repeat assessments;[2] a Pfizer supported study (Salvatoni A et al) tested the occurrence of sleep related breathing disorders in 12 patients with PWS before and after 6 weeks of somatropin treatment.[3]

The evaluators remarked, "Although video endoscopic evaluation showed no increase of tonsillar and adenoid size after GH treatment, it is important to note that [obstructive apnea index] did show an increase in 42% of patients. However, this study failed to provide any conclusive evidence due to small sample size and shorter duration of GH treatment in this study."

Recommendation by evaluator

The evaluators suggested certain changes to the PI, on the assumption that the Contraindication might be discarded in favour of more detailed precautions.

"The sponsor claims that the cases of deaths in PWS patients do not warrant the specific Contraindication due to heterogeneity in the cases. Based on data provided in this submission, it is difficult to arrive at any definite conclusions regarding association between GH treatment and the deaths reported in PWS patients. On the other hand, GH treatment may provide benefits if due vigilance is exercised and a strict protocol is followed regarding initiation and maintenance of GH treatment in children with PWS..."

The Contraindication "may" be removed.

Risk-Benefit Analysis

The Delegate noted that the problem with this application is that the removal of the Contraindication is based on data from heterogenous cases. The number of persons treated is significant and better case details should be collected prospectively. The TGA clinical evaluators suggested that due vigilance might see otherwise excluded patients (by reason of Contraindications) acquire some benefit. This speculation should be tested in a prospective study that compares high risk and lower risk patients with PWS.

The TGA evaluators' helpful suggestions concerning improving the Precautions were supported by the Delegate.

To return to Contraindications more generally, the Delegate noted that the document includes the following Contraindication:

"Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accident trauma, extensive burns or acute respiratory failure should not be treated with Genotropin (see Precautions regarding acutely critically ill patients on substitution therapy with Genotropin)."

The proposed Precautionary text is:

"The effects of Genotropin on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with

Genotropin 5.3 or 8 mg daily compared to patients receiving placebo (41.9 versus 19.3%). These types of patients should not be treated with Genotropin (see Contraindications). As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved. In all patients developing other or similar acute critical illness, the possible benefits of treatment with Genotropin must be weighed against the potential risk involved."

While the Delegate was not certain as to the sensitivity of adverse event detection, deaths are unable to be missed. The adverse experience in intensive care unit patients is such that it prevents Genotropin from finding its way into widespread unapproved use in the absence of these two Phase III studies described above. The studies were adequate and it might not be ethical to repeat them.

The implications for children with respiratory difficulties in PWS may be similar: serious stress may be exacerbated by somatropin. The pathogenic mechanism is not known and the only way to resolve this is via a prospective study. The numbers reported on in the current data set are impressive but the data are woolly and better data management is needed.

The Delegate proposed to permit the change of dosing regimen which is not controversial and which was previously approved.

The application to delete from the product information document the Contraindication,

Somatropin is contraindicated in patients with Prader-Willi Syndrome who are severely obese or have severe respiratory impairment (see Precautions)

should be declined due to inadequate data to support this change. The applicant was invited to conduct a prospective study with rigorous case ascertainment including high and lower risk patients. The Precautions should be revised as suggested.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposals.

ADEC recommended approval of the proposed change in dosing to revert to the previously approved dosing regimen.

ADEC recommended rejection of the submission to delete the Contraindication from the product information document on the grounds that the submitted data are deemed to be insufficient to support the change or to define the pathogenic mechanism in cases of deaths amongst patients with Prader-Willi Syndrome.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the change in dosing to express the dose in children as a weekly dose instead of a daily dose and to include instructions for the use of the Pfizer administration device (Genotropin Pen) with Genotropin cartridges.

The sponsor withdrew the application to delete the Contraindication in patients with Prader-Willi syndrome who are severely obese or who have severe respiratory impairment from the product information without prejudice before a decision was made.

PRODUCT INFORMATION

GENOTROPIN®

5 mg powder for injection with diluent (with preservative)

12 mg powder for injection with diluent (with preservative)

GENOTROPIN MiniQuick®

in strengths from 0.6 – 2.0 mg powder for injection with diluent (single dose syringes).

GENERIC NAME

Somatropin (rbe), recombinant human growth hormone.

DESCRIPTION

GENOTROPIN is produced using recombinant DNA technology; it is synthesised in bacteria, *Escherichia coli* K12 containing a modified pBR322 plasmid which expresses the gene for a prohormone consisting of the 191 amino acids of human growth hormone preceded by a 23 amino acid signal peptide. The signal peptide is removed by a specific signal peptidase located in the bacterial plasma membrane. The authentic human growth hormone is then harvested through careful disruption of the outer wall of the bacterium. The inner cell wall remains in principle intact. The subsequent purification process guarantees a pure final product with a content and sequence of amino acids identical with endogenous human pituitary growth hormone.

Reconstituted solution has an osmolality of approximately 300 mosm/kg and pH approximately 6.7.

PHARMACOLOGY

In vitro, preclinical and clinical tests have demonstrated that GENOTROPIN is therapeutically equivalent to human growth hormone of pituitary origin and achieves similar pharmacokinetic profiles in normal adults. In paediatric patients who have growth hormone deficiency or Prader-Willi Syndrome (PWS), treatment with GENOTROPIN stimulates linear growth and normalises concentrations of IGF-1 (insulin-like growth factor-1). In adults with growth hormone deficiency, treatment with GENOTROPIN results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism and normalisation of IGF-1 concentrations.

In addition, the following actions have been demonstrated:

Tissue Growth

Skeletal growth: GENOTROPIN stimulates skeletal growth in paediatric patients with growth hormone deficiency or PWS. The measurable increase in body length after administration results from an effect on the epiphyseal plates of long bones. Concentrations of IGF-1, which may play a

role in skeletal growth, are generally low in the serum of paediatric patients with growth hormone deficiency or PWS but tend to increase during treatment with GENOTROPIN. Elevations in mean serum alkaline phosphatase concentration are also seen.

Cell growth: It has been shown that there are fewer skeletal muscle cells in short-statured paediatric patients who lack endogenous hormone as compared with the normal paediatric population. Treatment with somatropin results in an increase in both the number and size of muscle cells.

Protein metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with GENOTROPIN.

Carbohydrate metabolism

Paediatric patients with hypopituitarism sometimes experience fasting hypoglycaemia that is improved by treatment with GENOTROPIN. Large doses of hormone may impair glucose tolerance.

Lipid metabolism

In growth hormone deficient patients, administration of somatropin has resulted in lipid mobilisation, reduction in body fat stores and increased plasma fatty acids.

Mineral metabolism

Somatropin induces retention of sodium, potassium and phosphorus. Serum concentrations of inorganic phosphate are increased in patients with growth hormone deficiency after therapy with GENOTROPIN. Serum calcium is not significantly altered by GENOTROPIN. Growth hormone could increase calciuria.

Body composition

Adult growth hormone deficient patients treated with GENOTROPIN at the recommended adult dose demonstrate a decrease in fat mass and an increase in lean body mass. When these alterations are coupled with the increase in total body water, the overall effect is to modify body composition, an effect that is maintained with continued treatment.

Pharmacodynamics

Most growth hormone deficient children have subnormal serum levels of IGF-1 which increase during growth hormone treatment. After GENOTROPIN administration an increase of IGF-1 levels has been shown both in healthy volunteers and in growth hormone deficient children.

Pharmacokinetics

Approximately 80% is absorbed following subcutaneous (sc) injection. Maximum serum concentrations are achieved around 5 hours following injection and the elimination half life is about 4 hours. GENOTROPIN is metabolised in both the liver and kidneys via protein catabolism.

The pharmacokinetic profile after an intramuscular injection (im) is similar to sc injection. No significant differences have been noted in tmax, Cmax or area under the curve (AUC) between these

two routes of administration. Moreover, biological effects on increasing non-esterified fatty acid and IGF-1 do not differ.

No significant difference has been noted in positive growth responses to growth hormone administration by either the im or sc route where the frequency of dosing is the same.

Clinical Trials

Turner Syndrome

Final height data are available on approximately 900 patients with Turner syndrome from 14 studies worldwide. The Kabi International Growth Study (KIGS; now the Pfizer International Growth Database) has contributed the largest number of patients at 168 with data collected from 28 countries. Other large series include USA, France and Australia with 166, 117 and 114 patients respectively. All 14 studies were uncontrolled and utilised historical control data and the method devised by Lyon of projected adult height for comparison with actual adult height in determining therapeutic efficacy.

A variety of adjunctive treatments including oestrogen replacement therapy and androgen therapy were used in the different studies. Age at introduction of concomitant oestrogen therapy varied. In one study with somatropin, concomitant oestrogen therapy commenced after age 15 years was associated with a 3.3 cm improvement in height compared with oestrogen therapy commenced after 12 years (p = 0.003). Androgen therapy was not shown to be of benefit in terms of increasing adult height.

The mean age at onset of somatropin therapy was relatively advanced, ranging from 9.2 to 13.1 years with 75% having a mean age of onset greater than 12 years. The estimated final height gain averaged across all studies (unweighted for the number of patients included in each study) was 5.4 cm, range 0 - 9.3 cm. Efficacy was demonstrated at doses of 0.160 to 0.375 mg/kg/week.

Prader-Willi Syndrome

The safety and efficacy of GENOTROPIN were evaluated in paediatric patients with Prader-Willi syndrome in two, non-blinded, randomised controlled clinical trials. Patients received either GENOTROPIN or they did not receive any treatment for the first year of the studies, while all patients received GENOTROPIN during the second year. GENOTROPIN was administered as a daily sc injection, and the dose was re-calculated at three month intervals for every patient. In study 1, the treatment group (n = 15) received GENOTROPIN at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group (n = 12) received GENOTROPIN at a dose of 0.48 mg/kg/week. In study 2, the treatment group received GENOTROPIN at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received GENOTROPIN at a dose of 0.36 mg/kg/week. This study was not conducted beyond 24 months.

Patients who received GENOTROPIN showed significant increases in linear growth during the first year of study compared with patients who received no treatment (Table 1). Linear growth continued to increase in the second year, when both groups received treatment with GENOTROPIN. Final height data are not available from these studies.

Table 1: Efficacy of GENOTROPIN in Paediatric Patients with Prader-Willi Syndrome (Mean + SD)

	Study 1		Study 2	
	GENOTROPIN (0.24 mg/kg/week) n=15	**Control n=12**	**GENOTROPIN (0.36 mg/kg/week) n=7**	**Control n=9**
Linear Growth (cm) Baseline height	112.7 ± 14.9	109.5 ± 12.0	120.3 ± 17.5	120.5 ± 11.2
Growth from months 0 to 12	11.6 ± 2.3 (p≤0.001)	5.0 ± 1.2	10.7 ± 2.3 (p≤0.001)	4.3 ± 1.5
Height Standard Deviation Score (SDS) for Age Baseline SDS	-1.6 ± 1.3	-1.8 ± 1.5	-2.6 ± 1.7	-2.1 ± 1.4
SDS change from 0 to 12 months	-0.5 ± 1.3 (p≤0.0001)	-1.9 ± 1.4	-1.4 ± 1.5 (p≤0.0015)	-2.2 ± 1.4

Changes in body composition were also observed in patients receiving GENOTROPIN in the first year of study compared with patients who did not receive any treatment. Available results for subjects in Study 1 are present in Table 2. These changes included a decrease in the amount of fat mass and increases in the amount of lean body mass and the ratio of lean-to-fat tissue, while changes in body weight were similar. Treatment with GENOTROPIN did not accelerate bone age, compared with patients who did not receive any treatment. Data to confirm the relationship between body composition changes due to growth hormone treatment and health outcomes in Prader-Willi syndrome patients are not yet available.

Table 2: Effect of GENOTROPIN on Body Composition in Paediatric Patients with Prader-Willi Syndrome (Mean ± SD)

	GENOTROPIN (n=14)	**Control (n=10)**
Fat mass (kg) Baseline	12.3 ± 6.8	9.4 ± 4.9
Change from 0 months to 12	-0.9 ± 2.2 (p≤0.0045)	2.3 ± 2.4
Lean body mass (kg) Baseline	15.6 ± 5.7	14.3 ± 4.0
Change from 0 months to 12	4.7 ± 1.9 (p≤0.009)	0.7 ± 2.4
Lean body mass/Fat mass Baseline	1.4 ± 0.4	1.8 ± 0.8
Change from 0 months to 12	1.0 ± 1.4 (p≤0.0026)	-0.1 ± 0.6
Body weight (kg)[#] Baseline	27.2 ± 12.0	23.2 ± 7.0
Change from 0 months to 12	3.7 ± 2.0 (p=0.57)	3.5 ± 1.9

\# n=15 for the group receiving GENOTROPIN; n=12 for the Control group

Adult Replacement Therapy

The effects of GENOTROPIN on growth hormone deficient adults were compared to placebo in 12 randomised clinical trials conducted in Europe and one multicentre study conducted in Australia. Each study included a six month, double blind period followed by a six month open label treatment period where all patients received GENOTROPIN.

The largest multicentre trial (n=163) included 55 patients with childhood onset growth hormone deficiency, and was designed to assess the effects of replacement therapy with GENOTROPIN. The primary objective was to determine the effects of long term use of GENOTROPIN on quality of life, using the Nottingham Health Profile (NHP). (The NHP is a general health related quality of life questionnaire.) Secondary objectives were to compare the effects of GENOTROPIN and placebo on body composition.

83 patients received GENOTROPIN and 80 received placebo for six months, followed by six months of active treatment. The GENOTROPIN dosage for the first month of therapy was 0.04 mg/kg/week, followed by 0.08 mg/kg/week, divided into 7 daily doses.

Body fat mass and fat free mass were determined by anthropometry and bioelectrical impedance analysis (BIA), and by dual X-ray absorptiometry (DEXA) in a subset of patients. Bone mineral density, total body potassium and total body protein were also measured, as well as waist to hip ratio, lipid profile, blood glucose and blood pressure.

Compared to placebo, GENOTROPIN treated patients experienced a decrease in peripheral and truncal skin fold thickness (p=0.02, p<0.001 respectively) after 6 months, with the majority of this effect seen in the first 3 months. Fat mass by DEXA was significantly reduced in the GENOTROPIN treated group compared to placebo (p<0.001) at 6 months and this was maintained at 12 months. Fat free mass (BIA) was significantly increased in the GENOTROPIN group at 6 months (from 50.6 kg to 53.6 kg $\pm$ 0.3 kg) but was unchanged for the placebo group (p<0.001). Again, the majority of this increase occurred in the first 3 months of treatment. Similar results were seen with DEXA measurements. Total body protein increased after 6 months treatment, from 9.8 kg to 10.4 kg $\pm$ 0.2 kg, but was not changed for the placebo group (p<0.001). There was no further increase at 12 months.

A significant decrease in the waist/hip ratio was seen in the treated group at 6 months (0.894 to 0.87 $\pm$ 0.003) compared to placebo (0.892 to 0.894 $\pm$ 0.002) (p=0.001). For the group receiving 6 months placebo, waist to hip ratio was significantly decreased at the 9 and 12 month measurements. Total cholesterol decreased after six months of treatment compared to placebo (p<0.05) but this difference was not maintained at 12 months. However, the lower LDL levels observed at 6 months (from 3.8 mmol/L to 3.3 mmol/L $\pm$ 0.1) were maintained at 12 months.

At 6 months there were no statistically significant differences between GENOTROPIN and placebo with respect to physical activity at work or leisure, days of sick leave, satisfaction with social life, and occurrence of significant life events. Overall changes in the NHP scales were small.

Chronic Renal Insufficiency

Four open-labelled, uncontrolled, multicentre studies evaluated the efficacy and safety of GENOTROPIN therapy in short prepubertal and pubertal children with chronic renal insufficiency (glomerular filtration rate of less than 50 mL/min/1.73 m^2) on conservative treatment or on dialysis (peritoneal dialysis and haemodialysis). Dosage of GENOTROPIN in all studies was equivalent to 1.43 mg/m^2/day, given as daily subcutaneous injections. The primary efficacy variable was growth

rate calculated as cm/year. Height was measured every 3 months, and change in height determined annually.

A total of 161 patients with chronic renal insufficiency and 101 on dialysis were studied. Following GENOTROPIN treatment growth velocity doubled in patients during the first year of treatment, and remained above baseline during the study observation period of up to 4 years for both prepubertal and pubertal patients (Table 3). This resulted in an improvement of height standard deviation score over the 4 year period.

Table 3: Height velocity, cm/year, in prepubertal and pubertal short children with chronic renal insufficiency before and during treatment with GENOTROPIN (Mean ± SD)

Study group	n	Pre-treatment	n	1st year	n	2nd year	n	3rd year	n	4th year
Prepubertal group										
96 10 834*	44	4.6 ± 1.8	44	8.8 ± 2.4	17	6.5 ± 2.2	7	6.5 ± 2.3		-
96 10 835**	16	3.0 ± 1.9	16	6.2 ± 3.4	6	5.6 ± 2.4	3	5.9 ± 2.2		-
97 10 028*	42	5.7 ± 2.8	42	9.9 ± 2.4	28	7.9 ± 1.6	19	7.3 ± 1.5	9	6.5 ± 1.2
97 10 087**	22	3.3 ± 2.4	22	7.1 ± 2.4	11	7.1 ± 1.2	7	5.6 ± 1.2		-
Pubertal group										
96 10 834*	14	4.7 ± 2.3	14	8.2 ± 2.6	8	7.0 ± 3.4	2	8.1 ± 3.4		-
96 10 835**	16	3.4 ± 2.4	16	7.4 ± 3.1	3	6.4 ± 1.8		-		-
97 10 028*	17	4.9 ± 1.8	17	8.1 ± 2.7	9	7.5 ± 2.1	4	5.9 ± 2.8		-
97 10 087**	19	3.5 ± 2.1	19	6.8 ± 3.0	13	5.9 ± 1.9	5	5.6 ± 3.0		-

* Study included patients with chronic renal insufficiency (glomerular filtration rate of less than 50 mL/min/1.73 m^2).
** Study included patients with chronic renal insufficiency undergoing peritoneal dialysis or haemodialysis

There was no difference in the incidence of adverse events compared with studies of GENOTROPIN in growth hormone deficient patients and in Turner Syndrome.

GENOTROPIN MiniQuick Range

The relative bioavailability of GENOTROPIN MiniQuick and GENOTROPIN 1.3 mg powder for injection with diluent was investigated in two separate single dose studies each comparing a single strength of the GENOTROPIN MiniQuick to GENOTROPIN 1.3 mg without preservative in a two-way crossover design. The second lowest strength, 0.4 mg, and the highest strength, 2.0 mg, of MiniQuick were selected to encompass the whole range. The dose of 0.03 mg/kg body weight was considered to result in too large an injection volume for the lowest MiniQuick strength, 0.2 mg, to be used. These studies were conducted with adult growth hormone deficient patients to remove possible variability and analytical error due to endogenous growth hormone. Patients were required to be abstinent from somatropin injections for at least one week before the start of the study.

Only AUC was used to test for bioequivalence which is appropriate as this parameter gives the best measurement of the total amount of substance delivered by injection. Both strengths of GENOTROPIN MiniQuick met the standard criterion for bioequivalence with GENOTROPIN in that the 90% confidence interval (CI) for ratio between test and reference preparations was between 0.80 and 1.25. The AUC ratio for 0.4 mg MiniQuick/GENOTROPIN was 0.894 (90% CI, 0.802 – 0.996) and for 2.0 mg MiniQuick/GENOTROPIN was 0.890 (90% CI, 0.809 – 0.978).

GENOTROPIN 5.3 mg and GENOTROPIN 12 mg

The bioequivalence of GENOTROPIN when a dose of 5.3 mg was administered from two different formulations, 5.3 mg and 12 mg, was investigated in a cross over design study in healthy male volunteers. GENOTROPIN 5.3 mg was found to be bioequivalent to GENOTROPIN 12 mg, in that the 90% confidence interval (CI) for ratio between test and reference preparations was between 0.80 and 1.25. The ratios for AUC_∞ and AUC_{0-24} of GENOTROPIN 12 mg to GENOTROPIN 5.3 mg were 1.06 (90% CI: 1.02-1.09) and 1.05 (90% CI: 1.01-1.09), respectively.

INDICATIONS

Short stature due to decreased or failed secretion of pituitary growth hormone.

Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL.

Growth disturbances associated with gonadal dysgenesis (Turner syndrome).

Improvement of body composition and treatment of short stature associated with Prader-Willi syndrome (PWS) in paediatric patients.

For treatment of growth disturbance in children with chronic renal insufficiency whose height is on or less than twenty-fifth percentile and whose growth velocity is on or less than twenty-fifth percentile for bone age. Chronic renal insufficiency is defined as glomerular filtration rate of less than 50 mL/min/1.73 m^2.

CONTRAINDICATIONS

GENOTROPIN should not be used in patients with active tumours or evidence of tumour growth. Anti-tumour therapy must be completed prior to starting therapy with GENOTROPIN.

It should not be used for growth promotion in children with closed epiphyses.

Known hypersensitivity to meta-Cresol is a contraindication for GENOTROPIN formulations with preservative as they contain meta-Cresol in the supplied diluent.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accident trauma, extensive burns or acute respiratory failure should not be treated with GENOTROPIN (refer PRECAUTIONS regarding acutely critically ill patients on substitution therapy with GENOTROPIN).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see PRECAUTIONS).

PRECAUTIONS

There have been reports of fatalities associated with the use of growth hormone in paediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. Another

possible risk factor may be male gender. Patients with Prader-Willi syndrome should be evaluated for upper airway obstruction before initiation of treatment with somatropin. If during treatment with somatropin patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted. All patients with Prader-Willi syndrome should be evaluated for sleep apnoea and monitored if sleep apnoea is suspected. These patients should also have effective weight control and be monitored for signs of respiratory infections, which should be diagnosed as early as possible and treated aggressively (see CONTRAINDICATIONS).

In patients with Prader-Willi syndrome, treatment should always be in conjunction with a calorie restricted diet. Experience with prolonged treatment in patients with PWS is limited.

Myositis is a very rare adverse event that may be related to the preservative meta-Cresol. In the case of myalgia or disproportionate pain at the injection site, myositis should be considered and, if confirmed, a GENOTROPIN presentation without meta-Cresol should be used.

Somatropin reduces insulin sensitivity and therefore patients should be observed for evidence of glucose intolerance. In rare cases the diagnostic criteria for diabetes mellitus type II may be fulfilled as a result of growth hormone therapy but risk factors such as obesity (including obese PWS patients), family history, steroid treatment or pre-existing impaired glucose tolerance have been present in most cases where this has occurred. Growth hormone can be used in patients with already manifest diabetes mellitus, however, its use requires special care and the dose of anti-diabetic therapy may require adjustment.

In growth hormone deficiency secondary to treatment of a malignant disease it is recommended to pay attention to signs of relapse of the malignancy.

Treatment in adults should be attempted only after a definitive treatment of pituitary tumour (if present) is completed, and after all other pituitary hormone deficiencies are corrected as clinically indicated.

During treatment with somatropin an enhanced T4 to T3 conversion has been found which may result in a reduction in serum T4 and an increase in serum T3 concentrations. In patients receiving replacement therapy with thyroid hormone mild hyperthyroidism may occur. It is therefore advisable to test thyroid function after starting treatment with somatropin and after dose adjustments.

In some patients hypothyroidism might develop during growth hormone treatment. Since untreated hypothyroidism may interfere with the response to somatropin, patients should have a periodic thyroid function test and should be treated with thyroid hormone when indicated.

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphysis of the hip may occur more frequently. Patients administered growth hormone should be observed for signs of limping as this may indicate development of slipped capital epiphysis.

Large doses of glucocorticoids may inhibit the growth promoting effect of growth hormone. Patients with co-existing ACTH deficiencies should have their glucocorticoid replacement doses carefully adjusted.

Somatropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins. Changes to serum levels of unbound serum cortisol have not been reported. The clinical relevance of these findings seems limited.

In patients with (pan) hypopituitarism, standard replacement therapy should be closely monitored.

Growth hormone treatment of patients with renal allograft may represent an increased risk for acute rejection in patients with two or more rejection episodes in their background history.

In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a fundoscopy 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 guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring, for symptoms of intracranial hypertension is necessary.

Progression of scoliosis can occur in patients who experience rapid growth. As growth hormone increases growth rate, physicians should be alert to this abnormality, which may manifest during growth hormone therapy. Scoliosis is commonly seen in patients with Prader-Willi syndrome.

The effects of GENOTROPIN on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5.3 mg or 8 mg GENOTROPIN daily compared to patients receiving placebo (41.9% versus 19.3%). These types of patients should not be treated with GENOTROPIN (refer CONTRAINDICATIONS). As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved. In all patients developing other or similar acute critical illness, the possible benefits of treatment with GENOTROPIN must be weighed against the potential risk involved.

Patients with childhood growth hormone deficiency should be retested for growth hormone deficiency before commencing treatment as adults.

Experience with prolonged therapy in adults is lacking.

Experience with patients over 60 years is lacking.

In chronic renal insufficiency, growth should be followed for a year preceding institution of therapy, to verify growth disturbance. Conservative treatment for renal insufficiency should have been established and should be maintained during treatment. The treatment should be discontinued at renal transplantation.

GENOTROPIN should be administered by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

Carcinogenicity, mutagenicity and impairment of fertility

Associations between elevated serum IGF-1 concentrations and risks of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known. Serum IGF-1 levels can be affected by factors other than growth hormone status including nutrition. There was no evidence for somatropin genotoxicity in assays for gene mutation in bacteria and mouse lymphoma cells or chromosomal damage in human lymphocytes and rat bone marrow cells.

Reproduction was inhibited in male and female rats at somatropin doses of 1 mg/kg/day or more, with reduced copulation and conception rates, lengthened or absent oestrus cycles and at 3.3 mg/kg/day, a lack of responsiveness of females to males, and slight reductions in sperm motility

and survival. Rat reproduction was unaffected by 0.3 mg/kg/day somatropin, which resulted in a systemic exposure (based on body surface area) of approximately twice that anticipated at maximal clinical dose.

Use in pregnancy (Category B2)

Somatropin was not teratogenic and did not affect fetal growth at subcutaneous maternal doses up to 3.3 mg/kg/day in rats or 1.3 mg/kg/day in rabbits, which resulted in systemic exposures based on body surface area of approximately 40-fold the anticipated maximum clinical exposure.

There is no experience with somatropin during pregnancy, nor has the need for such use been established.

Use in lactation

No information as to whether peptide hormones pass into the breast milk is available, but absorption of the intact protein in the gastrointestinal tract of the infant is extremely unlikely.

Interactions with other drugs

Data from an interaction study conducted in growth hormone deficient adults, suggest that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporin). The clinical significance of this is unknown.

See also precaution statements above regarding diabetes mellitus, thyroid disorder and ACTH deficiencies.

ADVERSE REACTIONS

Side effects have been noted in approximately 10% of the patients participating in clinical trials in children with short stature.

In clinical trials in adults, side effects have been noted in $30 - 40\%$ of patients, primarily related to symptoms of fluid retention, in both active and placebo treated groups. Dosage reduction reduced symptoms in some patients. Adverse reactions rarely influenced daily activities.

	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10 000, <1/1000	Very Rare <1/10, 000
Neoplasms, benign and malignant				Leukaemia
Immune system disorders	Formation of antibodies			
Endocrine disorders			Diabetes mellitus type II	
Nervous system disorders	In adults, paraesthesia	In adults, carpal tunnel syndrome. In children, paraesthesia	Benign intracranial hypertension	
Skin and subcutaneous tissue disorders	In children, transient local skin reactions			
Musculoskeletal, connective tissue and bone disorders	In adults, stiffness in the extremities, arthralgia, myalgia,	In children, stiffness in the extremities, arthralgia, myalgia		
General disorders and administration site disorders	In adults, peripheral oedema	In children, peripheral oedema		

In a series of 230 GENOTROPIN treated children, anti-hGH antibodies were detectable in only four children at 12 months (1.7%). The binding capacities of these antibodies have been low and without clinical significance, however, determination of antibody titre may be considered in those children who fail to respond to GENOTROPIN therapy.

After long term application of somatropin, an increased chromosome fragility has in one study been observed in lymphocytes from treated patients following in vitro addition of the radiomimetic drug bleomycin. The clinical significance of this finding is unclear.

Note: Some cases of acute leukaemia have been reported in growth hormone deficient children untreated as well as treated with growth hormone and might represent a slightly increased incidence compared with non growth hormone deficient children. A causal relationship to growth hormone therapy has not been established.

In the post-marketing experience, rare cases of sudden death have been reported in patients affected by Prader-Willi syndrome treated with somatropin, although no causal relationship has been demonstrated.

DOSAGE AND ADMINISTRATION

GENOTROPIN is administered by subcutaneous injection. The injection site should be varied in an attempt to prevent lipoatrophy. The weekly dose should be given in divided doses, 6 to 7 times per week.

Children with growth hormone deficiency: The diagnosis of growth hormone deficiency should be verified before the preparation is administered. This requires a thorough investigation of the pituitary function, including proper provocation tests. The dosage is individual and gradually titrated, but generally an initial dose of 0.175 to 0.245 mg/kg body weight per week is recommended.

Turner syndrome: A dose of 0.3 to 0.35 mg/kg body weight per week is recommended.

Prader-Willi syndrome: The diagnosis of PWS should be confirmed by appropriate genetic testing. Generally a dose of 0.245 to 0.35 mg/kg body weight per week is recommended.

Chronic renal insufficiency: A dose of 0.3 to 0.35 mg/kg body weight per week is recommended.

Adults with growth hormone deficiency: The recommended dosage at the start of therapy is 0.04 mg/kg/week divided into 7 daily subcutaneous injections. This dose should be gradually increased according to individual patient requirements to a maximum of 0.08 mg/kg/week. Dose titration is based on the development of side effects and determination of serum levels of insulin like growth factor (IGF-1). Dose requirements may decline with increasing age.

Bioequivalence has not been demonstrated for GENOTROPIN 5 mg or GENOTROPIN 12 mg administered in the GENOTROPIN Pen injection device and GENOTROPIN MiniQuick.

It is recommended that regular monitoring of growth rate and measurement of biochemical markers, such as IGF-1 levels, be undertaken to ensure adequate delivery of growth hormone and compliance with therapy.

Handling and Storage

The solution is prepared by screwing the reconstitution device or administration device together so that the diluent will be mixed with the powder in the two-compartment cartridge. Gently dissolve the drug with a slow swirling motion. Do not shake vigorously, this might cause denaturation of the active ingredient. When using an administration device the injection needle should be screwed on before reconstitution.

GENOTROPIN 5 mg and GENOTROPIN 12 mg

Store at 2 - 8°C (refrigerate, do not freeze). Protect from light. GENOTROPIN 5 mg and GENOTROPIN 12 mg are dispensed in special glass ampoules, so called two-compartment cartridges, with the active substance in one compartment and diluent in the other. GENOTROPIN 5 mg and GENOTROPIN 12 mg are intended for use in a Pfizer administration device. The Pfizer administration devices are colour coded, and **must** be used with the matching colour coded GENOTROPIN cartridge to give the correct dose: GENOTROPIN Pen 5 (green) **must** be used with GENOTROPIN 5 mg cartridge (green); GENOTROPIN Pen 12 (purple) **must** be used with GENOTROPIN 12 mg cartridge (purple).

The administration device with cartridge in use can be stored in the refrigerator for 28 days. It should not be carried in the shirt pocket or in a school bag but should be kept in the refrigerator at 2 - 8°C. Storage under 25°C for 1 month is possible within the proposed shelf life, prior to reconstitution.

GENOTROPIN MiniQuick 0.6 to 2.0 mg

Store at 2 - 8°C (refrigerate, do not freeze). Protect from light. GENOTROPIN MiniQuick is dispensed in a special glass ampoule, a so called two-compartment cartridge, with the active substance in one compartment and diluent in the other. If necessary, the product may be stored at or

below 25°C by the end-user for a single period of not more than 6 months. During and/or at the end of the 6 month period the product must be used or discarded. It should not be put back in the refrigerator. The reconstituted solution should be used immediately but can be stored at 2 - 8°C protected from light for up to 24 hours. Use in one patient on one occasion only. Contains no antimicrobial preservative.

OVERDOSAGE

No acute overdose or intoxication is known. Acute overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Long term overdosage could result in signs and symptoms consistent with the known effects of somatropin excess.

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

Contact the Poisons Information centre for advice on the management of an overdose.

PRESENTATION

After reconstitution, GENOTROPIN 5 mg with preservative, two-compartment cartridge contains:
- somatropin (rbe) 5 mg
- glycine 2 mg
- mannitol 41 mg
- sodium phosphate-monobasic 280 μg
- sodium phosphate-dibasic anhydrous 270 μg
- meta-Cresol 3 mg
- water for injections to 1 mL

After reconstitution, GENOTROPIN 12 mg with preservative, two-compartment cartridge contains:
- somatropin (rbe) 12 mg
- glycine 2 mg
- mannitol 40 mg
- sodium phosphate-monobasic 410 μg
- sodium phosphate-dibasic anhydrous 400 μg
- meta-Cresol 3 mg
- water for injections to 1 mL

After reconstitution, GENOTROPIN MiniQuick, two-compartment cartridge contains:
- somatropin (rbe) 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 or 2.0 mg
- glycine 0.21 mg

- mannitol 12.5 mg

- sodium phosphate-monobasic 45 μg

- sodium phosphate-dibasic anhydrous 25 μg

- water for injections to 0.25 mL

Availability

GENOTROPIN 5 mg powder for injection with diluent (1 mL): 1s, 5s.

GENOTROPIN 12 mg powder for injection with diluent (1 mL): 1s, 5s.

GENOTROPIN MiniQuick powder for injection with diluent (0.25 mL) in strengths of 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 or 2.0 mg: 7s

Not all pack sizes may be marketed.

SPONSOR

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Date of TGA approval: 15 November 2007

Date of most recent amendment: 19 January 2010

Date of AAT Consent Order: 26 November 2001 (on the decision to register the above mentioned products for the treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak growth hormone concentrations of less than 2.5 nanogram/mL).