NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Human growth hormone in children (review of NICE technology appraisal guidance 42)

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

Growth hormone (GH), which is also known as somatropin, is a hormone produced by the anterior pituitary gland. GH is essential for normal growth in children. It increases growth by a direct action on the growth plates (the area between the epiphysis and the diaphysis within which bone growth occurs) and by production of insulin-like growth factors (especially IGF-1) mainly in the liver. Growth failure in children can be a result of GH deficiency but is also a prominent characteristic of Turner syndrome, Prader–Willi syndrome, chronic renal insufficiency), children born small for gestational age and short stature homeobox-containing gene deficiency.

1.1.1 Growth hormone deficiency

GH deficiency occurs when the pituitary gland fails to produce enough GH. It is the most common endocrine cause of short stature. GH deficiency may occur as an isolated hormonal deficiency or in combination with multiple pituitary hormone deficiency arising from hypopituitarism, tumours in the central nervous system, cranial irradiation or other organic causes. In many cases the cause of the deficiency is unknown (idiopathic GH deficiency). The UK Child Growth Foundation estimates that idiopathic GH deficiency occurs in about 1 in every 3800 births, but reliable figures are difficult to obtain for GH

deficiency associated with other causes. Children with GH deficiency who do not receive treatment have a final adult height of 134–146 cm for men and 128–134 cm for women.

1.1.2 Turner syndrome

Turner syndrome is a chromosomal disorder occurring in girls characterised by the complete or partial lack of one X chromosome. The two most common clinical characteristics are short stature and ovarian failure. Girls with Turner syndrome do not have a deficiency in natural GH secretion, although they may have a relative lack of sensitivity to GH. Not all girls with Turner syndrome need GH treatment. The incidence of Turner syndrome is between 1 in 1500 and 1 in 2500 live female births. Most girls with Turner syndrome have short stature and if untreated girls have a final adult height of 136–147 cm. The average adult height deficit of 20 cm in women with Turner syndrome is mostly because of haploinsufficiency of the short stature homeobox-containing gene.

1.1.3 Prader–Willi syndrome

Prader–Willi syndrome is a genetic disorder caused by an abnormality of the paternally derived chromosome 15. Common clinical characteristics include hypogonadism, short stature, hypotonia, dysmorphic features, hypoventilation, abnormal body composition, obesity and obesity-related diseases, and behavioural problems. Children with Prader–Willi syndrome often have reduced GH secretion, and this may be linked to obesity. The incidence of Prader–Willi syndrome is between 1 in 15,000 and 1 in 25,000 live births. Children with Prader–Willi syndrome who are untreated with GH reach a final height of 154 cm for men and 145–159 cm for women.

1.1.4 Chronic renal insufficiency

Chronic renal insufficiency (CRI), also known as chronic renal failure, is defined as a persistent elevation of serum creatinine and/or urea. It can be caused by a variety of conditions, including congenital disorders, glomerular disorders and infections. Growth failure is a complication of CRI and usually

begins when the glomerular filtration rate falls to 50% of normal. Growth failure becomes a significant problem when the glomerular filtration rate falls below 25% of normal. After kidney transplantation, chronic graft rejection and treatment with steroids can restrict growth and development.

Not all patients with CRI in childhood will be shorter than average, but figures from the UK Renal Registry indicate that 29% of transplant patients and 41% of dialysis patients are below the second percentile for height. Children with congenital disorders (approximately 60% of children with CRI) are of normal length at birth, but are below the 3rd percentile for height within their first year and remain on this 3rd percentile parallel to normal percentiles throughout childhood.

1.1.5 Growth disturbance in children born small for gestational age

There are various thresholds for defining a child as being born 'small for gestational age', the most commonly used being a birth height or weight that is 2 SD (standard deviations) or more below the population average, or is below the tenth percentile for birth weight. There are several possible causes but these can be categorised into maternal causes (age, parity, medical conditions, smoking, malnutrition, alcohol misuse) and placental and fetal causes (chromosomal abnormalities and genetic defects). The diagnosis of small for gestational age can be complicated, requiring accurate knowledge of gestational age and accurate measurements of the newborn's weight, length and head circumference, and a comparison with reference data. Children classified as being born small for gestational age may have concurrent diagnoses, such as familial short stature, Turner syndrome, GH deficiency or skeletal dysplasia.

More than 80% of babies born small for gestational age will start to achieve catch-up growth (growth velocity greater than the median for chronological age and gender) within the first 6 months and catch-up growth will be completed within the first 2 years. However, babies born prematurely who are small for gestational age might need 4 years in order to achieve growth catch-

up. It has been estimated that approximately 10% of children born small for gestational age remain at a height below -2 SD of the mean height for their age throughout childhood.

1.1.6 Short stature homeobox-containing gene deficiency

The short stature homeobox-containing gene (*SHOX*) is located on the distal ends of the X and Y chromosome and plays an important role in long bone growth. Normal growth requires two functional copies of the gene. Growth impairment can be caused by having a single functional copy of the *SHOX* gene, with the other copy being inactivated by mutation or deleted (haploinsufficiency). Common clinical characteristics associated with *SHOX* deficiency include disproportionate shortening of the middle sections of the limbs, bowing of the forearms and lower legs, and arm bone abnormality. *SHOX* deficiency can cause short stature in people with conditions such as Turner syndrome, Leri–Weil syndrome and dyschondrosteosis.

A small study that compared 26 people with *SHOX* haploinsufficiency with 45 of their unaffected relatives and general population standards found that the group with *SHOX* haploinsufficiency had a mean length that was 2.14 SDS (standard deviation score) less than unaffected relatives (3.8 cm shorter) at birth and 2.1 SDS throughout childhood. Girls were more severely affected than boys, with women's final height being 2.4 SDS (14.4 cm) shorter than unaffected siblings, and men's final height being 0.8 SDS (5.3 cm) shorter. It is not clear whether the group with *SHOX* haploinsufficiency had concurrent diagnoses.

1.2 Current management

GH therapy is currently the only active treatment option for growth failure in children with GH deficiency, Turner syndrome, CRI, Prader–Willi syndrome, in short children born small for gestational age and in children with *SHOX* deficiency. The place of GH treatment in the treatment pathway depends on the child's particular condition and age at diagnosis. The timing of GH treatment depends on the underlying pathology. For girls with Turner syndrome, oxandrolone may be added to GH treatment. In the UK,

conservative management strategies for CRI include advice on diet and nutritional supplementation.

NICE technology appraisal guidance 42 recommends GH therapy as option to help increase growth for children with GH deficiency, for girls with Turner syndrome, children with Prader–Willi syndrome and prepubertal children with CRI. It is also recommended as an option to improve body composition in children with Prader–Willi syndrome. Further details of the NICE technology appraisal guidance 42 are in appendix B; for the full guidance see www.nice.org.uk/TA42

When NICE technology appraisal guidance 42 was issued in 2002 somatropin had UK marketing authorisation for the treatment of children with GH deficiency, Turner syndrome, Prader–Willi syndrome and CRI. The UK marketing authorisations have since changed to include short children born small for gestational age and growth failure associated with *SHOX* deficiency.

2 The technology

Somatropin (table 1) is a synthetic form of human GH that is produced by recombinant DNA technology. It has a sequence identical to that of human growth hormone produced by the pituitary gland.

The dosage and the administration of somatropin should be tailored for each child. The recommended dosage varies according to the condition being treated: 23–29 micrograms/kg daily or 0.7–1.0 mg/m² for GH deficiency; 45–50 micrograms/kg daily or 1.4 mg/m² daily for Turner syndrome and CRI; 35 micrograms/kg daily or 1.0 mg/m² daily for growth disturbance in children born small for gestational age; 35 micrograms/kg daily or 1.0 mg/m² daily (with a maximum of 2.7 mg daily) for Prader–Willi syndrome; and 0.045–0.050 mg/kg daily for *SHOX* deficiency. Somatropin is self-administered at home, usually as a subcutaneous injection, 6–7 times a week.

Table 1 Summary description of technology

Proprietary name	Non-proprietary name	Manufacturer	Acquisition cost (BNF edition 57)
Humatrope	Somatropin	Eli Lilly	£18.00 per mg
Zomacton	Somatropin	Ferring	£19.92per mg
NutropinAq	Somatropin	Ipsen	£20.70 per mg
Norditropin Simple Xx	Somatropin	Novo Nordisk	£21.39 per mg
Genotropin	Somatropin	Pfizer	£23.19 per mg
Omnitrope[a]	Somatropin	Sandoz	£18.26 per mg
Saizen	Somatropin	Merck Serono	£23.18 per mg

[a] Omnitrope is a 'similar biological medicinal product'. A biological medicinal product is a new biological product that is similar to a medicine that has already been authorised to be marketed (the 'biological reference medicine') in the European Union. The active substance of a biosimilar medicine is similar, but not identical, to the biological reference medicine. Genotropin is the biological reference medicine for Omnitrope.

The UK marketing authorisations for somatropin for the following conditions can be summarised as follows (for the different products the wording may differ):

- growth disturbance in children due to insufficient secretion of growth hormone (GH deficiency).
- growth failure in girls associated with gonadal dysgenesis (Turner syndrome).
- growth retardation in prepubertal children associated with chronic renal insufficiency (CRI).
- children with Prader–Willi syndrome, for improvement of growth and body composition. The diagnosis of Prader–Willi syndrome should be confirmed by appropriate genetic testing.
- growth disturbance (current height SDS −2.5 and parental adjusted height SDS, −1) in short children born small for gestational age, with a birth weight and/or length below −2 SD, who did not show catch-up growth (height velocity SDS less than 0 during the past year) by 4 years of age or later.
- growth failure associated with *SHOX* deficiency, as confirmed by DNA analysis.

Seven manufacturers have UK marketing authorisations for the various indications (table 2).

Table 2 Indications for the use of somatropin in children

Indication	Growth hormone deficiency	Turner syndrome	CRI	Prader-Willi syndrome	Born small for gestational age	*SHOX* deficiency
Manufacturer (product)						
Eli Lilly (Humatrope)	✓	✓	✓		✓	✓
Ferring Pharmaceuticals (UK) (Zomacton)	✓	✓				
Ipsen (NutropinAq)	✓	✓	✓			
NovoNordisk (Norditropin Simple Xx)	✓	✓	✓		✓	
Pfizer (Genotropin)	✓	✓	✓	✓	✓	
Sandoz (Omnitrope[a])	✓	✓	✓	✓	✓	
Merck Serono (Saizen)	✓	✓	✓		✓	

[a] Omnitrope is a similar biological medicinal product

CRI, chronic renal insufficiency; *SHOX*, short stature homeobox-containing gene**.**

Adverse events may include headache, visual problems, nausea and vomiting, fluid retention (peripheral oedema), arthralgia, myalgia, paraesthesia, antibody formation, hypothyroidism and reactions at injection site. Particular attention should be paid to treating children with risk factors associated with diabetes mellitus, slipped capital epiphyses, idiopathic intracranial hypertension and malignancies.

According to a survey of endocrine clinics published in 2006 by the British Society of Paediatric Endocrinology and Diabetes[1], 4758 people received GH therapy in the UK, of whom 4168 were in England and Wales. The results suggested that 57.4% of people receiving GH therapy in the UK were treated for GH deficiency (around 2731 people), 18.7% for Turner syndrome (around

[1] Kirk J,Clayton P. Specialist services and transitional care in pediatric endocrinology in the UK and Ireland. *Clinical Endocrinology* 2006;65: 59-63.

890 people), 4.6% for Prader–Willi syndrome (around 219 people), 5.2% for being born small for gestational age (around 247 people), 2.5% for CRI (around 119 people), and 11.6% for other diagnoses (around 552 people). It is possible that the number of children with CRI who received GH was underestimated because some children with CRI are treated in nephrology rather than paediatric endocrine clinics. The number of patients treated with GH for *SHOX* deficiency was not reported in the survey and published figures are not available. Expert opinion indicates that very few patients with *SHOX* deficiency are currently receiving GH therapy (for example, only two of about 350–400 patients receiving GH in one unit are being treated for this).

3 The evidence

3.1 Clinical effectiveness

3.1.1 Manufacturers' submissions

Six out of the seven manufacturers submitted clinical effectiveness evidence on GH as a treatment for children with short stature. The submission from Sandoz did not include a systematic review but reported phase III studies comparing its product (Omnitrope) with the reference technology (Genotropin). The submission did not present clinical effectiveness compared with no treatment. Sandoz stated that the studies confirmed the long-term efficacy and safety of Omnitrope for GH treatment relative to the reference technology (Genotropin, Pfizer).

Novo Nordisk undertook a systematic review on behalf of five collaborating manufacturers (Lilly, Ipsen, Novo Nordisk, Pfizer and Merck Serono) to identify trials on all the licensed indications for somatropin since NICE technology appraisal guidance 42. Novo Nordisk identified 24 studies investigating the use of GH in the treatment of children with GH deficiency (11 studies), CRI (4 studies) and Turner syndrome (9 studies). Each manufacturer supplemented the studies identified by Novo Nordisk with studies that were specific to their own product or for indications not covered in the systematic review.

Overall the five collaborating manufacturers concluded that the studies demonstrated the clinical effectiveness of GH for all the licensed indications, with significant improvements reported in terms of height outcomes, body composition and metabolic markers. The manufacturers highlighted the lack of data on growth as an outcome and on quality of life in the studies. The Assessment Group's commentary on the search strategies used and on the studies identified can be found in appendix 8 (pages 251–261) of the assessment report.

Lilly undertook a literature search on the impact of short stature on quality of life in adolescents and adults of working age on behalf of the five collaborating manufacturers. One study, Christensen et al. (2007) was identified. The study is discussed in more detail on page 25 of the overview. The study reported poorer quality of life with greater height deficit and concluded that short stature in adulthood may be associated with a significant reduction in quality of life.

3.1.2 Assessment Group

Systematic review of existing clinical effectiveness evidence

The Assessment Group identified three systematic reviews: One carried out for NICE technology appraisal guidance 42, a Cochrane review relating to that appraisal, and a new systematic review of GH in Turner syndrome undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2007.

NICE technology appraisal guidance 42

The systematic review included randomised controlled trials (RCTs) comparing GH with placebo or no treatment in children with GH deficiency, Turner syndrome, CRI and Prader–Willi syndrome. In addition, non-randomised studies were included when final height data were not available from the RCTs. The Assessment Group concluded that although the quality of evidence was variable, there was evidence that GH treatment could increase short-term growth and improve final height. Results suggested that effects of GH on short-term growth velocity (1 year) could range from no improvement

to approximately 1 SD above the normal growth velocity for children of the same age. Final height gains for treated children over untreated children appeared to range from approximately 3 to 11 cm (GH deficiency 8–11 cm; Turner syndrome 5 cm; CRI 3–9 cm; Prader–Willi syndrome 10–11 cm;).

CADTH systematic review

The review included 19 RCTs or comparative observational studies that compared GH with placebo or no treatment, included females with Turner syndrome, measured growth (final height, interim height, growth velocity), adverse events and quality of life. The review found that growth was accelerated and height increased in girls taking GH for Turner syndrome. No serious adverse events were reported and no evidence was found to suggest that GH improves quality of life.

Assessment Group's systematic review

The Assessment Group conducted a systematic review for RCTs conducted in children with growth disturbance, according to the marketing authorisations for somatropin (see table 2) with the exception of small for gestational age for which no RCTs meeting the inclusion criteria were identified. See page 35 of the assessment report for details of the amended criteria for small for gestational age. Studies were included that compared the effectiveness of somatropin with management strategies without somatropin.

A total of 28 RCTs in 34 publications were identified. Further details of the RCTs are provided in table 3 on page 39 of the assessment report. The review undertaken by the Assessment Group excluded a number of studies that were included in NICE technology appraisal guidance 42 and the CADTH review. The Assessment Group's explanation for excluding the studies can be found on pages 40 (relating to NICE technology appraisal guidance 42) and 85-86 (relating to the CADTH review) of the assessment report.

The included studies reported at least one of the following outcomes: final height; height gained/height standard deviation score (height SDS); growth velocity/growth SDS; body composition; biochemical/metabolic markers and adverse events. None of the studies reported quality of life. The Assessment

Group stated that a meta-analysis was not appropriate because of heterogeneity in study design and participants.

For conciseness only growth outcomes and adverse events for GH deficiency, Turner syndrome, CRI, small for gestational age and *SHOX* deficiency are presented in the overview. For Prader–Willi syndrome a concise summary of body composition outcomes is also presented.

Growth hormone deficiency

One RCT (n =77) met the inclusion criteria for this review. This RCT had been considered for NICE technology appraisal guidance 42. The study recruited two groups of children with GH deficiency and one group of children without GH deficiency. The study used a dose of 15 U/m^2/week, and the Assessment Group stated that it is not clear how this corresponds to the licensed dose. The Assessment Group considered the overall quality of the reporting of the study to be mixed, with insufficient information given to allow assessment of the method of randomisation and blinding to the treatment allocation.

The study reported growth velocity, height SDS and biochemical markers as outcome measures (see pages 48–49 of the assessment report). Growth outcomes are presented in table 3.

Table 3 Growth outcomes for growth hormone deficiency

Study	Mean (SD)	GH	No treatment	p value
Soliman et al. (1996)	height standard deviation score[a]	−2.3 ± 0.45	−2.8 ± 0.45	p < 0.05
	Growth velocity (cm/year)	8.4 ± 1.4	5.7 ± 1.8	p < 0.05
[a] height relative to distribution of height in children of the same chronological age (or bone age if specified).				

Children in the treated group grew an average of 2.7 cm/year faster than those receiving no treatment in the 12 months of the study, and the difference between groups was statistically significant (p < 0.05). Similarly children in the treated group had a statistically significantly higher height SDS.

Turner syndrome

Six RCTs (n = 154, 89, 12, 9, 58 and 232) met the inclusion criteria for this review. All of the studies have been published since NICE technology appraisal guidance 42. Two of the included studies were of a cross-over design. Of the four remaining studies, two compared GH treatment with no treatment, one with low-dose oestrogen, and one with placebo. All studies included at least one treatment arm with a dose that was broadly comparable to the licensed dose of 45–50 micrograms/kg/day or 1.4 mg/m^2/day. Five of the six trials recruited broadly similar age groups, but the sixth specifically recruited very young girls with Turner syndrome.

The Assessment Group considered the reporting and methodological quality of the studies to be poor. Of the six included studies, one reported adequate randomisation to treatment groups, one study described adequate concealment of treatment allocation and one adequately blinded the patient to treatment by administering placebo. None of the included studies employed an intention-to-treat analysis (ITT).

Four of the six included studies reported growth outcomes and the key measures are presented in table 4. Details of the body composition outcomes and biochemical markers reported are provided on pages 47–49 of the assessment report.

Table 4 Growth outcomes for Turner syndrome studies

Study	Outcomes (mean ± standard deviation)	Growth hormone	Control	p value
Stephure and Canadian Growth Hormone Advisory Committee 2005 Protocol completion	Height (cm)	147.5±6.1	141.0 ± 5.4	p < 0.001
	Change in height (cm)	28.3 ± 8.9	19.0 ± 6.1	p < 0.001
	HtSDS (age-specific turner)	1.4 ± 1.0	0.2 ± 0.9	p < 0.001
	HtSDS (adult Turner)	0.7 ± 0.9	−0.3 ± 0.8	p < 0.001
	Change in HtSDS (age-specific Turner)	1.6 ± 0.6	0.3 ± 0.4	p < 0.001
Stephure and Canadian Growth Hormone Advisory Committee 2005 Addendum follow-up)	Height (cm)	149.0 ± 6.4	142.2 ± 6.6	p < 0.001
	Change in height (cm)	30.3 ± 8.3	21.6 ± 6.2	p < 0.001
	HtSDS (age-specific Turner)	0.9 ± 0.9	−0.1 ± 1.0	p < 0.001
	HtSDS (adult Turner)	0.9 ± 0.9	−0.1 ± 1.0	p < 0.001
	Change in HtSDS (age-specific Turner)	1.1 ± 0.5	0.0 ± 0.5	p < 0.001
Davenport et al. (2007)	Height (cm)	99.5 ± 7.6	91.9 ± 7.2	< 0.0001
	HtSDS	−0.34 ± 1.10	−2.16 ± 1.22	< 0.0001
	Height velocity (cm/year)	8.4 ± 1.6	5.5 ± 1.8	< 0.0001
	Height velocity standard deviation score	0.70 ± 1.11	−1.63 ± 1.29	< 0.001
Johnston et al. (2001)	Change in HtSDS in first year	+0.7 (0.7)	+0.4 (0.9)	< 0.05
Quigley et al. (2002) Study Group 1:GH 0.27 mg/kg/wk 2: GH 0.36 mg/kg/wk	Height velocity 0–18 months (cm/year)	1: 6.6 ± 1.1 2: 6.8 ± 1.1	4.2 ± 1.1	< 0.001
HtSDS, height standard deviation score – height relative to distribution of height in children of the same chronological age (or bone age if specified).				

The two studies reporting final height as an outcome found a statistically significant difference for height between the treated and untreated groups at the end of the studies ($p < 0.0001$). Three studies reported change in height SDS as an outcome measure and found a higher change in height SDS in the treated than the untreated group. Height velocity was statistically significantly greater in the treated groups in the three studies that reported it as an outcome. This was greater in the first year and fell in the second year in both treatment groups where this was reported separately.

Adverse events were reported in four of the studies. One found greater levels of adverse events in the treated group, one found similar levels across

groups, one found significantly higher levels of or worsening of otits media. One reported seven participants with coincidental disorders and four withdrawals because of problems with adherence, but gave no further details.

Prader–Willi syndrome

Eight RCTs (n = 32, 54, 104, 20, 43, 14, 19, 29) in 13 publications met the inclusion criteria for this review. Three of these had been considered for NICE technology appraisal guidance 42 and five were new studies that had been published since the guidance. Seven of the studies were RCTs that compared 1 mg/m^2/day GH with no treatment for 1 or 2 years. One study was a cross-over RCT that compared 0.043 mg/kg/day GH with placebo injections, with participants spending 6 months in each treatment group. The doses used in the included studies reflect the various marketing authorisations for GH. Two studies reported results for infants and toddlers aged between 1 and 2.5 years. The remaining studies were in children aged between approximately 6 and 10 years.

The Assessment Group considered the reporting of the studies to be poor and to lack information on the method of randomisation or concealment of allocation. Only two of studies reported results on an ITT basis. Only one study reported a sample size calculation.

Six studies reported growth velocity SDS or an indicator of linear growth while 2 studies focused on body composition and biochemical markers and did not report any measure of change in height.

Growth and body composition outcomes are presented in tables 5 and 6 respectively. For details of the biochemical markers reported see pages 59–61 of the assessment report.

In the one study that reported changes in height, infants who received GH for a year grew an average of 6.2 cm more than those in the untreated group ($p < 0.001$). Two studies reported a statistically significant difference in height SDS between treated and untreated participants. The difference was 1 SDS (favouring GH treatment) in one study and > 2 SDS (year 2) in the other.

Three studies reported growth velocity as an outcome. Children treated with GH grew 3 cm/year faster than untreated children in one study and 5 cm/year faster in another. Another study reported a positive growth velocity SDS for children treated with GH and a negative growth velocity for untreated children (5.5 versus −2.3). The differences between groups were statistically significant in all three studies. Two of the included studies reported bone age as an outcome measure, and this was similar in both treatment groups.

Four studies reported a statistically significantly lower percentage of body fat (between 1 and 10% lower) in children treated with GH compared with no treatment or placebo. Three studies reported that children treated with GH had statistically significantly higher lean body mass or a larger improvement in lean body mass than untreated children. One study reported that lean body mass was significantly better in treated than in untreated children. Studies reporting BMI had mixed results. Two studies found that BMI was statistically significantly lower in children treated with GH than in untreated children. However, another study found no statistically significant difference between the two groups, and three more studies did not report a p value for between-group statistical significance.

Table 5 Growth outcomes for Prader-Willi syndrome

Study	Outcomes (mean ± SD)	Growth hormone	Control	p value
Carrel et al. (2001)	Change in height (cm)	15.4 ± 2.3	9.2 ± 3.2	p < 0.001
	Height SDS	−0.2 ± 1.5	−1.5 ± 0.7	NR
	Growth velocity SDS	5.0 ± 1.8	1.2 ± 1.4	NR
Carrel et al. (1999) Myers et al. (1999)	Height SDS	−0.6 ± 1.2	−1.6 ± 1.2	p < 0.01
	Mean growth velocity (cm/year)	10.1 ± 2.5	5.0 ± 1.8	p < 0.01
	Mean growth velocity SDS	4.6 ± 2.9	−0.7 ± 1.9	p < 0.01
de Lind van Wijngaarden et al. (2009) Festen et al. (2008) (infants)	Height SDS median (IQR)	−0.9 (−1.6 to −0.1)	−1.8 (−3.5 to −1.4)	0.003
	Δ Height SDS median (IQR)	1.2 (1.0 to 1.6)	−0.2 (−0.6 to 0.3)	< 0.0001
de Lind van Wijngaarden et al. (2009) Festen et al. (2008)(children)	Height SDS median (IQR)	−0.5 (−0.8 to 0.0)	−2.6 (−3.4 to −2.3)	< 0.0001
	Δ Height SDS median (IQR)	1.4 (1.3 to 1.8)	−0.1 (−0.4 to 0.1)	< 0.0001
Festen et al. (2007)	Height SDS median (IQR)	−0.6 (−0.9 to −0.3)	−3.0 (−3.5 to −1.8)	NR
Festen et al. (2007)	Height SDS median (IQR)	−1.6 (−2.1 to −0.8)	−2.3 (−3.9 to −1.5)	NR
Haqq et al. (2003)	Height SDS	−1.2 ± 1.1	−1.3 ± 1.3	NR
	Growth velocity (cm/year)	7.5 ± 3.5	4.5 ± 2.7	p < 0.05
Hauffa (1997)	Height SDS	1.07	−0.25	NR
	Height velocity SDS	5.5	−2.3	p = 0.0012
Lindgren et al.(1998) Lindgren et al. (1997)	Height SDS mean (range)	−0.4 (−2.7 to 1.9)	−1.8 (−5.1 to 0.2)	NR
	Height velocity (SDS) mean ± SD (range)	6.0 ± 3.2 (1.4 to 11.9)	−1.4 (−3.2 to 0.3)	NR

Growth velocity SDS, growth velocity relative to distribution of growth velocity in children of the same chronological age (or bone age if specified); height SDS, height relative to distribution of height in children of the same chronological age (or bone age if specified); SDS, standard deviation score; IQR, Interquartile range; Δ, difference in; NR, not reported.

Table 6 Body composition outcomes for Prader-Willi syndrome studies

Study	Outcomes (mean±SD)	Growth hormone	Control	p value
Carrel et al. 2004	Mean % body fat	23.2 ± 8.9	32.7 ± 8.8	0.03
	Change in body fat(	−4.8% ± 5.7%	+4.1% ± 4.6%	p = 0.001
	Change in lean body mass (kg)	3.6 ± 0.5	1.8 ± 0.7	p < 0.001
Carrel et al. (1999) Myers et al. (1999)	Body fat (%)(	38.4 ± 10.7	45.8 ± 8.8	p < 0.01
	Lean mass (kg)	25.6 ± 4.3	21.7 ± 5.0	p < 0.01
	BMI (kg/m^2)	23.7 ± 6.3	25.2 ± 8.9	
de Lind van Wijngaarden et al.(2009) Festen et al. (2008) (infants)	BMI (kg/m^2)	16.3 (15.7 to 18.2)	16.4 (15.4 to 19.8)	nr
	BMI (SDS)	0.3 (−0.1 to 1.6)	0.3 (−0.6 to 1.6)	0.72
de Lind van Wijngaarden et al. (2009) Festen et al. (2008) (children)[a]	BMI (kg/m^2)	17.5 (16.1 to 21.1)	19.1 (17.8 to 20.8)	
	BMI (SDS)	1.1 (−0.2 to 1.7)	1.4 (1.1 to 1.6)	0.19
	Fat % (SDS)	1.9 (0.7 to 2.3)	2.4 (2.1 to 2.7)	p < 0.001
	Fat (SDS)	1.1 (0.6 to 2.0)	4.5 (0.9 to 2.0)	p < 0.01
	Lean body mass $_{age}$ (SDS)	−0.1 (−1.3 to 0.6)	−2.5 (−3.8 to −1.4)	p < 0.001
	Lean body mass $_{HtSDS}$	−1.9 (−2.4 to −1.4)	−2.3 (−2.7 to −1.3)	p < 0.05
Festen et al. (2007)	BMI (kg/m^2)	16.3 (15.8 to 19.0)	18.5 (17.5 to 20.6)	p < 0.05
	BMI SDS	0.4 (−0.3 to 1.1)	1.2 (0.9 to 1.5)	p < 0.05
	Lean body mass SDS	−1.2 (−1.7 to −1.1)	−2.8 (−3 to 1.9)	nr
	Percent fat SDS	1.7 (0.9 to 1.9)	2.1 (1.9 to 2.4)	nr
Festen et al. (2007)	BMI (kg/m^2)	16.4 (15.2 to 18.5)	15.5 (14.9 to 17.6)	nr
	BMI SDS	0.3 (−0.9 to 1.8)	−0.4 (−0.8 to 1.3)	nr
	Body fat (%)	22.5 (11.3 to 33.2)	22.8 (19.5 to 32.9)	nr
	Lean body mass (%)	74.8 (63.7 to 82.3)	73.6 (61.6 to 75.9)	nr
Haqq et al (2003)	BMI (kg/m^2)	31.2 ± 8.9	32.8 ± 9.7	p < 0.05
	BMI (SDS)	2.4 ± 0.5	2.5 ± 0.6	nr
	Body fat (%))	49.7 ± 5.8	54.1 ± 5.6	p < 0.05
	Fat mass (kg)	26.1 ± 12.8	29.1 ± 14.1	p < 0.05
	Lean mass (kg)	24.1 ± 8.8	22.4 ± 8.5	p < 0.05

Study	Outcomes (mean±SD)	Growth hormone	Control	p value
Lindgren et al. (1998 and 1997)	BMI (SDS)	2.0 (−2.4 to 6.7)	2.5 (0.1 to 6.1)	nr
	Body fat (%)	30.9± 11.4	38.2± 9.1	nr

[a] n = unclear for many of these outcomes

BMI, Body mass index; SDS, standard deviation score; HtSDS, height standard deviation score.
nr, not reported;

None of the studies reported adverse events in any detail. Three of the studies did not report adverse events at all. No serious adverse events were reported in the five studies that presented data on this.

Chronic renal insufficiency

Six RCTs (n = 203, 125, 20, 11, 69, 23) met the inclusion criteria for this review. Four of these had been considered for NICE technology appraisal guidance 42 and two were new studies that had been published since the guidance. The included RCTs were of different designs (two cross-over studies and four parallel-group studies). Three of the parallel-group RCTs were open label, with the comparator groups receiving no treatment. One was placebo controlled. The two cross-over studies had placebo and treatment phases, although there does not appear to have been a wash-out phase in either of the trials. Three of the studies investigated GH treatment in children who had received a kidney transplant at least 1 year before starting the study and the other three studied children who had CRI.

The Assessment Group considered the reporting of the trials to be poor. None of the included studies provided clear information on method of randomisation, concealment of allocation or on whether or not outcome assessors were blinded to participants' treatment groups. Five of the studies did not present results on an ITT basis. The Assessment Group also stated that there was a lack of clarity around primary outcomes and power calculations and that the trials may have been underpowered to detect differences in outcomes relating to growth and body composition.

All of the studies reported growth outcomes (table 7). See pages 68–70 of the assessment report for details of body composition outcomes and biochemical and metabolic markers.

Table 7 Growth outcomes for CRI studies

Study	Outcomes (mean± SD)	Growth hormone	Control	p value
Broyer et al. (1996)	Change in HtSDS	+0.6 ± 0.3	+0.1 ± 0.3	p < 0.0001
	Change in growth velocity (cm/year)	3.7 ±1.6	0.3 ± 1.6	p < 0.0001
Fine et al. (2004)	HtSDS	−1.6	−2.9	nr
	Growth velocity (cm/year)	7.8 ± 2.1 (n = 55)	5.5 ± 1.9 (n = 27)	p < 0.00005
Powell et al. (1996)	Height gain (cm)	9.1 ± 2.8	5.5 ±1.9	p < 0.0001
	HtSDS change from baseline	0.8 ± 0.5	0.0 ± 0.3	p < 0.0001
Sanchez et al. (2002)	HtSDS	−1.1 ± 1.0	nr	nr
	Annual growth velocity (cm/year)	8.0 ± 2.1	4.8 ± 1.7	p < 0.01
Hokken-Koelega et al. (1991)	growth velocity (cm/6 months)	1: 5.2 (1.2) 2: 4.4 (1.6)	1: 1.5 (0.4) 2: 2.4 (1.0)	p < 0.0001
	Height velocity SDS	1: 6.9 (2.4) 2: 5.0 (4.5)	1: −3.0 (1.6) 2: −0.5 (3.2)	p < 0.0001
Hokken-Koelega et al. (1996)	Growth velocity (cm/6 months)	1: 5.3 (1.0) 2: 3.9 (1.3)	1: 1.5 (0.9) 2: 1.9 (0.7)	p < 0.0001
	Height velocity SDS	1: 9.1 (2.9) 2: 5.3 (4.0)	1: −1.3 (2.9) 2: −0.4 (1.7)	p < 0.0001

HtSDS, height standard deviation score – height relative to distribution of height in children of the same chronological age (or bone age if specified); nr, not reported; SDS, standard deviation score.

The study that reported height gain found that children treated with GH grew an average of 3.6 cm more than those who were untreated at 1 year (9.1 cm versus 5.5 cm, p < 0.0001). Two studies reported that height SDS was statistically significantly better in children treated with GH than those who were not. Five studies reported that change in growth velocity or growth velocity SDS was statistically significantly faster for children who received GH treatment than for those children who did not. The between-group differences in velocity ranged from 3.2 cm/year to 4.2 cm/year in the parallel-group trials. Two studies reported that there was no statistically different difference in bone age between the treated and untreated participants. Two studies reported

small differences with slightly lower mean ages for GH treatment overall compared with placebo, but did not present any p values for these comparisons. One study reported that the change in bone age between baseline and 2 years was greater in children treated with GH who completed both years of the study than in untreated children.

No serious adverse events were reported in the four studies that presented data on this.

Children born short for gestational age

Six RCTs met the amended inclusion criteria for the review. The mean ages in five of the studies ranged from 4.7 (2.3–6.3) to 6.3 (4.0–8.0) years. The sixth study included older children with mean ages of 12.7 ± 1.4 years in the GH–treated and 12.8 ± 1.6 years in the control group. Only one study included a treatment arm with the licensed dose, the other studies all used approximately two or three times the UK licensed dose. Four of the studies stated a treatment duration of 2 years. One study administered GH for an average of 2.7 ± 0.6 years, until the participants reached adult height. The children in the other study received treatment for 2 years, but only the first year allowed a randomised comparison between GH and no treatment.

The Assessment Group considered the studies to be of poor methodological quality. In most studies it was not clear whether the assignment to treatment groups was truly random and whether the outcome assessors and care providers were blinded. In each of the studies blinding of the participant was inadequate because no placebo was used. Only one study conducted an ITT analysis.

All six studies reported growth outcomes (table 8). For details of body composition outcomes and biochemical and metabolic markers see pages 77–80 of the assessment report.

Table 8 Growth outcomes for studies of children born small for gestational age

Study	Outcomes (mean± SD)	Growth hormone	Control	p value
Phillip et al. (2009)	HtSDS	1. −2.3 ± 0.6 2. −1.8 ± 0.8	−3.0 ± 0.6	nr
	Change in HtSDS	1. 0.8 ± 0.3 2. 1.4 ± 0.4	0.1 ± 0.3	nr
	Additional height gained[a] (cm)	1. 3.3 ± 0.2 (95% CI 2.9 to 3.7) 2. 6.5 ± 0.2 (95% CI 6.0 to 6.9)	n/a	nr
Carel et al. (2003)	Adult height total height gain (cm)	26 ± 7	22 ± 6	0.005
	End of treatment: HtSDS	−2.1 ± 1.0	nr	nr
	Adult height HtSDS	−2.1 ± 1.0	−2.7 ± 1.0	0.005
	Adult height total height gain SDS	1.1 ± 0.9	0.5 ± 0.8	nr
	Adult height difference from target HtSDS	−0.9 ± 1.2	−1.7 ± 1.2	0.005
De Schepper et al. (2007)	HtSDS year 2	−1.7 ± 0.7	−3 ± 1	< 0.0001
de Zegher et al. (1996)	Gain in HtSDS	1: 2.1 ± 0.1 2: 2.5 ± 0.1	0.2 ± 0.1	< 0.001[b]
	Gain in HtSDS for bone age	1: 1.0 ± 0.2 2: 1.2 ± 0.4	0.0 ± 0.3	< 0.05[b]
	Growth velocity (cm/yr)	1: 10.2 ± 0.2 2: 11.0 ± 0.4	5.7 ± 0.3	< 0.001
	Growth velocity SDS	1: 4.3 ± 0.3 2: 5.2 ± 0.4	−0.9 ± 0.3	< 0.001[b]
de Zegher et al. (2002)	HtSDS	−1.8 (−3.9 to −0.5)	−3.0 (−3.3 to −2.5)	nr
	Growth velocity (cm/year)	8.5 (6.3 to 10.2)	5.6 (4.4 to 6.8)	nr
Lagrou et al. (2008)	HtSDS	−1.9 ± 0.7	−3.1 ± 0.9	< 0.001

[a] compared with untreated controls

[b] untreated vs. treated

95% CI, 95% confidence interval; HtSDS, height standard deviation score – height relative to distribution of height in children of the same chronological age (or bone age if specified); nr, not reported; SDS, standard deviation score.

One study reported total gain in adult height, and found this was approximately 4 cm in people who had received GH. The difference between

groups was statistically significant ($p < 0.005$). Adult height gain SDS was also statistically significantly higher in people who had received GH. However, the study used a dose that was approximately twice the licensed dose, and the study was of children with a mean age of 12.7 years at start of treatment. The Assessment Group stated that this is may limit the generalisability of the results. One study reported that children who received 0.033 mg/kg/day GH (the licensed dose) gained an additional 3.3 cm in height compared with untreated children, and those who received 0.1 mg/kg/day gained 6.5 cm after 1 year's treatment. Height SDS was statistically significantly higher in children treated with GH in two studies, and higher (but with no reported p value) in two others. Growth velocity (cm/year) was greater in the treated groups at the end of year 2 in the two studies that reported this outcome, but the difference was only reported to be statistically significant in one. One study reported bone age. The gain in bone age (years) was statistically significantly greater in the groups receiving GH than those who were untreated.

Four of the studies reported limited detail on adverse events. One study reported two events in treated children but did not discuss if these led to discontinuation of the drug. A second study reported only that there were 'no noteworthy' adverse events recorded. A third study reported four serious adverse events that were not linked to the study drug. In the remaining study, three were linked to GH and resolved/stabilised once treatment was discontinued.

***SHOX* deficiency**

One study of children with *SHOX* deficiency met the inclusion criteria for the review. The 2-year multicentre RCT compared a daily injection of 50 micrograms GH with no treatment in 52 pre-pubertal children with confirmed *SHOX* deficiency. The Assessment Group stated that because the study did not report the mean baseline weight of participants it was not possible to comment on whether or not the study reflects use of the licensed dose. The mean age of the groups in the study was 7.5 ± 2.7 years for the treated group and 7.3 ± 2.1 years for the untreated group. The Assessment Group considered the study to be poorly reported, with little information on

method of randomisation or concealment of allocation. The analysis was not reported on an ITT basis. The study did not include discussion of sample size or a power calculation, and therefore the Assessment Group stated that it was not possible to determine whether or not it was adequately powered to detect a difference in the primary outcome (first year growth velocity).

Growth outcomes are presented in table 10. The Assessment Group's commentary on the biochemical markers reported can be found on page 83 of the assessment report.

Table 10 Growth outcomes for *SHOX* deficiency study

Study	Outcomes (mean ± SD)	Growth hormone	Control	p value
Blum et al. (2007)	height gain (cm)	16.4 ± 0.4	10.5 ± 0.4	< 0.001
	height SDS	−2.1 ± 0.2	−3.0 ± 0.2	< 0.001
	height velocity (cm/year)	7.3 ± 0.2	5.4 ± 0.2	< 0.001
	height velocity SDS	2.3 ± 0.3	−0.4 ± 0.1 (n = 22)	< 0.001
SDS, standard deviation score.				

By the end of the second year, children treated with GH had gained statistically significantly more height than those in the control group, with no statistically significant difference in catch-up of bone age. Height SDS was statistically significantly higher in treated than in untreated children. Treatment with GH led to a statistically significantly greater growth velocity in both years 1 and 2 (3.5 cm/year greater than in untreated children in year 1, and 1.9 cm/year greater in year 2). The height velocity SDS was positive (that is, above the average for chronological age) during both years of GH treatment whereas untreated children had a negative height velocity SDS.

GH treatment in children with *SHOX* deficiency was not associated with any serious adverse events in this study.

Summary of clinical effectiveness

- GH deficiency: children treated with GH group grew 2.7 cm/year faster than children in the untreated group and had a statistically significantly higher height SDS after 1 year (−2.3 ± 0.45 versus −2.8 ± 0.45).
- Turner syndrome: girls in one study grew an average of 9.3 cm more than untreated girls. In a study of younger children, the difference was 7.6 cm after 2 years. Height SDS values were statistically significantly higher in treated than in untreated girls.
- Prader–Willi syndrome: Infants who received GH for a year grew significantly taller (6.2 cm more) than those in the untreated group in the only study to report change in height. Two studies reported a statistically significant difference in height SDS in favour of GH. GH-treated children had statistically significantly higher lean body mass and lower body fat than untreated participants in three studies. Effects on BMI were mixed.
- CRI: in a 1-year study GH-treated children grew an average of 3.6 cm more than untreated children. Height SDS was statistically significantly higher in treated than in untreated children in two studies.
- Small for gestational age: no studies met the original inclusion criteria for the review, so these were amended to include children from the age of 3 years with no catch-up growth, with no reference to mid parental height. Only one of the six included studies used the licensed dose; the others used doses two or three times higher. Adult height was approximately 4 cm higher in GH-treated people in the only study to report this outcome ($p < 0.005$). Adult height gain SDS was also statistically significantly higher in the group treated with GH in this study. Mean Height SDS was higher in treated than untreated children in four other studies, significantly so in two of these.
- *SHOX* deficiency: After 2 years of treatment, children were approximately 6 cm taller than the control group and height SDS was statistically significantly higher in treated than in untreated children.

Quality of life

None of the studies in the Assessment Group's systematic review reported quality of life as an outcome. Further searches identified six studies that met the Assessment Group's inclusion criteria. Two of these studies reported changes in quality of life using preference-based measures. The first study used the time trade off (TTO) methodology for people with GH deficiency, Turner syndrome and CRI. The Assessment Group identified a number of limitations of this study and concluded that it did not provide robust estimates of utility gain from GH treatment. The second study used a regression model to give utility weights (based on the EQ–5D from a UK population) to the disease-specific quality of life assessment of GH deficiency in adults. As the study was specific to GH deficiency, the Assessment Group considered it unlikely that the study would be generalisable to the other conditions for which GH is licensed.

The Assessment Group undertook an additional search for data on quality of life in relation to height. The Assessment Group identified one study by Christensen et al. (2007) that provided utility estimates based on the EQ–5D for different height SDS from the Health Survey for England for an adult general population (14,416 adults). Inter-relationships between variables were assessed using ordinary least squares (OLS) linear regressions, controlling for age, weight and gender. There was a positive correlation between an increase in height and a participant's EQ-5D score. The mean EQ-5D scores were lower in people who were shorter compared with those who were taller, as well as lower than the overall population mean. The authors of the study performed an analysis of variance (ANOVA) combined with post hoc Tukey HSD test for homogeneous subgroups and identified that there were three significantly different subgroups in terms of EQ-5D scores. A multivariate linear analysis using the identified subgroups were undertaken to predict the variation in health related quality of life. The study is discussed in more detail in the cost effectiveness section on pages 29 and 35 of the overview.

The Assessment Group concluded that there was likely to be a small gain in utility for people receiving GH treatment. However, this was based on a proxy

measure of gain in height from shorter people in the general population. The Assessment Group stated that this excludes many relevant potential benefits of GH treatment such as improvement in body composition and lipid profiles.

Other evidence from professional/patient groups and nominated experts

Patient and professional groups reported that when a child starts GH therapy, the choice of GH product is based upon a discussion between the clinician and child/carer. Because there is no evidence that any one GH product has efficacy or safety benefits over another, the choice of product is dependent upon the choice of delivery system and the support package offered by the manufacturer. However, patient groups have highlighted their concerns regarding the safety of similar biological products. The British Society of Paediatric Endocrinology and Diabetes reported that patient adherence may be improved by patient choice; however there appears to be no specific features that determine what GH product a patient will choose.

The British Society of Paediatric Endocrinology and Diabetes highlighted that there are many confounding factors in childhood that make assessing quality of life difficult and that there is an on-going study examining changes in quality of life in children receiving GH treatment.

3.2 Cost effectiveness

3.2.1 Model used for NICE technology appraisal guidance 42

The economic evaluation undertaken for NICE technology appraisal guidance 42 consisted of separate cost-effectiveness models comparing GH treatment with no GH treatment (defined as growth monitoring) for each condition under review. This analysis estimated under base case conditions the cost per centimetre gained in final height was approximately £6000 for GH deficiency, from £15,800 to £17,300 for Turner syndrome, from £7400 to £24,100 for CRI, and approximately £7030 for Prader–Willi syndrome (2000 prices).

3.2.2 Review of published cost-effectiveness studies

The Assessment Group identified two North American economic evaluations for GH treatment for children with Turner syndrome (Canadian Agency for Drugs and Technologies in Health, 2007) and with GH deficiency (Joshi et al, 2006) published since the economic evaluation for NICE technology appraisal guidance 42. Further details on these economic evaluations, and the Assessment Group's commentary, can be found on pages 86–92 of the assessment report.

The economic evaluation of GH in children with Turner syndrome estimated an incremental cost-effectiveness ratio (ICER) of C$243,078 per quality-adjusted life year (QALY) gained. The economic evaluation of GH in children with GH deficiency estimated ICERs of approximately US$37,000 per QALY for the 5- to 16-year-old cohort and approximately US$42,600 per QALY gained for the 3- to 18-year-old cohort.

The Assessment Group stated that the two different estimates of cost effectiveness were largely because of choice of utility estimates (the utility increment associated with GH treatment ranged from 0.04 to 0.189) and assumptions on effectiveness. The Assessment Group considered the economic evaluation undertaken by the CADTH to be of higher quality because the effectiveness of the treatment had been established through a systematic review and the estimates for parameter values were considered more appropriate. The Assessment Group concluded that because there is a lack of reliable estimates of utility gains associated with GH treatment, the results of both economic evaluations should be treated with caution.

3.2.3 Manufacturers' models

Six out of the seven manufacturers submitted cost-effectiveness evidence. The Assessment Group stated that the cost-effectiveness evidence submitted by Sandoz did not comply with the NICE reference case requirements as it appears to be a cost-minimisation analysis using Genotropin as a comparator. The submission contained a comparison of the annual cost of treatment with Omnitrope and with Genotropin in people with GH deficiency and Turner

syndrome. The Assessment Group's critique of the submission can be found in appendix 10 on pages 263–264 of the assessment report.

Five out of the six manufacturers (Lilly, Ipsen, Novo Nordisk,Pfizer and Merck serono) collaborated on developing a core de novo economic model to estimate the cost-effectiveness of GH treatment in children with GH deficiency, Turner syndrome, Prader–Willi syndrome, CRI and small for gestational age. The model was developed by Pfizer. It was based on the model for NICE technology appraisal guidance 42 but was extended to consider longer-term outcomes to estimate cost effectiveness in terms of cost per QALY gained.

Each of the collaborating manufacturers presented essentially the same model with some minor modifications (for example changes in the unit price of somatropin). Two manufacturers (Merck Serono and Novo Nordisk) produced their own version of the model. Merck Serono's economic model included a waste elimination model to examine the costs savings that were most likely to occur by using the Easypod device rather than other delivery systems, so the health benefits differ slightly from the other models. Novo Nordisk constructed a decision tree model to assess the cost effectiveness of GH treatment for the four indications that Norditropin is licensed for: GH deficiency, Turner syndrome, CRI and small for gestational age. The assumptions underpinning it, source of clinical effect, and utility data were identical to those in the core economic model.

Manufacturers' core model

A Markov cohort model was chosen for the economic evaluation. The decision model had three arms: treatment; no treatment and discontinue treatment. The modelled health states were 'alive' and 'dead' and transitions between these were determined using UK-specific mortality profiles observed in the general population. The economic model considered a cycle length of 1 year. In each cycle, a proportion of the cohort would exit the model based on mortality data from UK life tables, with the remainder of the cohort continuing

to the next model cycle. Costs and benefits were calculated for each cycle length according to the proportion of the cohort remaining in each cycle.

Two alternative model structures were also presented. An alternative model structure that allowed for the second clinical effect (a reduction in the risk of osteoporosis) was presented in a scenario analysis for GH deficiency. In this model it was assumed that a proportion of children with GH deficiency would continue treatment until they reach the age of 25 years. The cost-effectiveness analysis of GH treatment in Prader–Willi syndrome was based on an alternative structure of the model which assumed that people with Prader–Willi syndrome and diabetes would have a 10% lower quality of life than those without diabetes. It was assumed that the prevalence of diabetes in people with Prader–Willi syndrome would be reduced from 8% to 2%.

The utility scores used in the model in children with GH deficiency, Turner syndrome, CRI and small for gestational age were based on the study by Christensen et al. (2007) discussed on page 25 of the overview. A gain in height was assumed to be associated with quality of life improvements, which was assessed using the EQ–5D utility scale. The utility scale in the study was reported in terms of height SDS intervals of approximately 0.5 (range<-3 to 2.5). The utility gain in the Prader–Willi syndrome model was based on a small study (Bertella et al, 2007) of 13 adults with Prader–Willi syndrome who received GH for 2 years and a further utility gain for the reduced diabetes risk. Further details of the study are provided on page 97 of the assessment report.

The clinical effect and many of the other parameters used in the model were estimated from the Kabi International Growth (KIGS) observational database, which is a large-scale collaborative database developed by Pfizer for the safety and efficacy of treatment with GH. The dataset includes more than 60,000 treated people in over 50 countries for all licensed indications of Genotropin (that is, GH deficiency, Turner syndrome, Prader–Willi syndrome, small for gestational age and CRI). As *SHOX* deficiency is not a licensed indication of Genotropin, it is not included in the KIGS database. The input parameters used in the manufacturers' core model that had been derived from

the KIGS database are provided in table 36 on page 101 of the assessment report. The costs used in the model were based upon those used in the model for NICE technology appraisal guidance 42 and were inflated to current prices where appropriate. The mean daily per patient cost for each manufacturer's GH treatment was based upon the unit cost shown in table 1.

The base-case analyses for Pfizer, Lilly, Ipsen and Merck Serono are shown in table 11. One-way deterministic sensitivity analyses showed that the ICERs were most sensitive to choice of utility values, time horizon, discount rates, treatment duration, levels of treatment at the transition phase, the proportion of patients achieving final height, and drug price and/or drug dose.

The base-case results for the Novo Nordisk model using KIGS data are shown in table 12. Novo Nordisk also reported alternative ICERs using patient-level data. One-way sensitivity analyses showed that the ICERs were most sensitive to the discount rates used for outcomes and to changes in the utility scores associated with height SDS bands.

. Table 11 Base-case results for Pfizer, Lilly, Ipsen and Merck Serono

		GHD continued[a]	GHD	Turner syndrome	PWS	CRI	SGA
	Incremental QALY	3.483	3.483	2.825	2.3	2.526	2.98
	Height gain (cm)	32.24	32.24	7.95	25.59	4.48	21.92
Pfizer	Incremental Cost	£72,003	£61,124	£84,078	£74,849	£40,325	£54,088
	ICER (£/QALY)	£20,673	£17,552	£29,757	£32,540	£15,962	£18,167
	Cost per cm gain	£2,233	£1,896	£10,576	£2,925	£9,001	£2,467
Eli Lilly	Incremental Cost		£57,043	£65,654		£31,574	£42,340
	ICER (£/QALY)		£16,176	£36,237		£12,498	£14,221
	Cost per cm gain		£1,747	£8,258		£7,048	£1,932
Ipsen	Incremental Cost	£65,198	£54,779	£75,243		£36,129	
	ICER (£/QALY)	£18,721	£15,730	£26,630		£14,301	
	Cost per cm gain	£2,022	£1,699	£9,464		£8,065	
Merck Serono[b]	Incremental Cost	£72,719 *£65,711*		£84,077 *£75,847*		£40,325 *£36,416*	£54,087 *£48,839*
	ICER (£/QALY)	£20,881 *£18,869*		£29,757 *£26,844*		£15,962 *£14,414*	£18,167 *£16,404*
	Cost per cm gain	£2,256 *£2,038*		£10,576 *£9,540*		£9,001 *£8,129*	£2,467 *£2,228*

[a] GHD continued is the scenario with growth hormone treatment during childhood and a transition period.

[b] Figures in italics for EasyPod device.

CRI, chronic renal insufficiency; GHD, growth hormone deficiency; ICER, incremental cost effectiveness ratio; PWS, Prader-Willi syndrome; QALY, quality adjusted life year; SGA, Small for gestational age.

Table 12 Base-case results for Novo Nordisk using KIGS database

	GHD continued[a]	GHD	Turner syndrome	CRI	SGA
Incremental QALY	3.7	3.7	2.89	2.9	2.77
Height gain (cm)	27.45	27.45	7.95	3.65	5.67
Incremental **c**ost	£71,264	£58,637	£79,976	£41,388	£51,745
Cost per QALY	£19,276	£15,861	£27,720	£14,254	£18,655
Cost per cm gain	£2,596	£2,136	£10,060	£11,345	£9,123

[a] GHD continued is the scenario with growth hormone treatment during childhood and a transition period.

CRI: chronic renal insufficiency; GHD: Growth hormone deficiency; QALY: quality adjusted life years; SGA: Small for gestational age

The Assessment Group highlighted the following concerns and uncertainty regarding the manufacturers' core model:

- The clinical effectiveness estimates for height gain were taken from an observational cohort rather than an RCT. The Assessment Group stated that it was not clear whether the subset of the KIGS database chosen was representative of the UK patient population or, for example, whether the subset chosen may have more severe growth restriction.
- For three of the conditions (GH deficiency, Prader–Willi syndrome and small for gestational age) the estimates of height were considerably higher than those shown in the trials because of the estimates used for end height in the control group.
- For all conditions, except Prader–Willi syndrome, mortality rates from the general population were used. The Assessment Group stated that it was likely that people with the other conditions, in particular CRI, would have shorter life expectancy than the general population.
- The manufacturers used the study of Christensen et al. (2007) for their health-related quality of life utility values, but did not take these from the regression analysis in the study. Instead they used the relationship between EQ–5D and height without controlling for other factors. The Assessment Group stated that utility gain attributed to height is likely to be capturing the combined effects of other (unobserved) variables, such as

age, long-standing illness and gender. Not controlling for other factors, in particular age, results in the overestimation of the utility values.

- The Assessment Group stated that there was high uncertainty associated with the assumptions and sources used to estimate quality of life gain in the Prader–Willi syndrome model. These were based on a small study of adults with Prader-Willi syndrome. It was unclear how this related to the quality of life gain for children and whether this benefit would be maintained throughout their lifetime. The methods used to derive utility values from the SF–36 were based on rating scales and therefore did not use choice-based methods in line with the NICE reference case. The Assessment Group stated that there are considerable difficulties in extrapolating the benefit from treating children with GH to their health benefits as adults.

3.2.4 Current Assessment Group's model

The Assessment Group developed a decision analytic model for the economic evaluation of GH for treatment of GH deficiency, Turner syndrome, Prader–Willi syndrome, CRI, small for gestational age and *SHOX* deficiency. This was based upon the model developed for NICE technology appraisal guidance 42. The Assessment Group's model compared a cohort of people receiving GH during their childhood with a cohort of who were not treated with GH. The state-transition Markov model had a cycle length of 1 year and a life-time horizon (100 years). The base-case decision analytic model included health states for alive and dead. The mortality rates for the population in England and Wales were applied in each cycle with an adjustment using the standard mortality rates for each of the conditions. Further details of the sources of the life expectancy data are provided on pages 110–111 of the assessment report. A 3.5% discount rate was used for benefits and costs.

An additional scenario was undertaken for GH deficiency where it was assumed that 34% of people with GH deficiency continued treatment until age 25 years with a dose of 0.4 mg/day. These people did not receive any additional benefit associated with height gain from this treatment in the model.

Effectiveness data

For GH deficiency, CRI, Prader–Willi syndrome and small for gestational age, the Assessment Group used data from the KIGS database for the start and end age of treatment, and duration of treatment. Because *SHOX* deficiency was not included in the KIGS database, the Assessment Group assumed that these children started treatment at the same age as those in the study by Blum et al. (2007) and continued treatment for the same duration as for children with Turner syndrome in the KIGS database. Further details of the study by Blum et al. (2007) are provided on page 82 of the assessment report. Further details on the start and end age of treatment, and the duration of treatment are shown in table 41 on page 112 of the assessment report.

The clinical effect of GH was taken from the systematic review in section 3, pages 31–84 of the assessment report. Where possible, the Assessment Group took the clinical effect from the best quality RCT in which children had treatment for a sufficiently long time to capture height SDS height gain, which the Assessment Group assumed would be at least 2 years. For GH deficiency, these data were not available, so data from the KIGS database were used to estimate the clinical effect. For small for gestational age, there were no RCTs available for the licensed dose and so the Assessment Group used data from a study with 1 year of treatment. For Turner syndrome, height gain was reported in terms of age-specific Turner syndrome height SDS, but the mean age-specific value was not reported. The Assessment Group assumed that the age-specific Turner syndrome height SDS was that reported in the KIGS database. The Assessment Group stated that a number of studies had not reported the height gain in centimetres. For these studies the Assessment Group converted height SDS values to centimetres using the height table from the Health Survey for England 2003.The clinical effect parameters and values used in the Assessment Group's model are provided in table 42 on page 113 of the assessment report.

A review of adherence to GH treatment was conducted by Merck Serono as part of the manufacturers' submissions. Based on a study identified by Merck Serono, the Assessment Group assumed an adherence rate of 85%.

Health-related quality of life data

As in the manufacturers' model, the Assessment Group used data from the study by Christiansen et al. (2007). The Assessment Group assumed that people in the treated and untreated cohorts would have no difference in terms of age, gender, social class, weight and long-standing illness. The differences in health-related quality of life utility estimates between the treated and untreated cohorts were therefore derived from their differences in height. According to the regression analysis, for those people shorter than −2.0 height SDS, an improvement of 1 height SDS will result in a change in health-related quality of life utility of 0.061. For the subgroup between −2.0 and 0.0 height SDS, a 1 height SDS improvement increases utility by 0.01. These values were used in the Assessment Group's estimation of cost effectiveness.

For people with Prader–Willi syndrome, there may be an additional health benefit associated with improved body composition. Any improvements in body composition may lead to reduced risk of diabetes and cardiovascular disease. The Assessment Group stated that there was considerable difficulty in estimating the magnitude of this effect and extrapolating short-term treatment in childhood to lifelong benefit. Because of the high uncertainty around the estimates of health-related quality of life benefit, the Assessment Group assumed no benefit associated with a change in body composition in the base case and then conducted a scenario analysis using a study by Hakim et al (2008) which estimated change in utility scores based on the unit change in BMI values.

Estimation of costs

The costs used in the Assessment Group's model were based on those used in the model for NICE technology appraisal guidance 42. The annual cost of monitoring associated with each condition was calculated for each arm of the model using treatment pathways described in NICE technology appraisal guidance 42. Treatment costs were calculated on the basis of mean dose of GH. Based on clinical opinion, the nurse visit time was assumed to be the same for all conditions and it was assumed that patients would have two outpatient visits per year. All children are monitored until they reach

adulthood, which was assumed to be 17 years of age. The unit costs and resource use are shown in tables 43 and 44 respectively on page 115 of the assessment report

The cost of the drug used in the manufacturers' models varied between £18 and £23.19 per mg. The Assessment Group assumed an average drug cost of £21.06 in the base case (see page 1 of the addendum to the assessment report) and varied the price in sensitivity analysis (see page 4 of the addendum to the assessment report). Drug costs were calculated according to the dosage used (table 45 on page 116 of the assessment report) and the weight of the child. The weight of children at different ages was taken from the KIGS database (appendix 13 on page 271 of the assessment report).

Results of Assessment Group's economic analysis

Table 13 shows the base case results. The cost effectiveness of GH therapy versus no treatment varied from £23,196 for GH deficiency to £135,311 for Prader–Willi syndrome per QALY gained. A further analysis was undertaken to investigate the effect of continuation of GH treatment into adulthood (to the age of 25 years) for 34% of the original cohort. These people did not receive any additional benefit associated with height gain from this treatment in the model. The results of the analysis are shown in table 14.

Table 13 Cost-effectiveness results for the base-case analysis

Condition		Costs (£)	QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	cm gain	ICER (£/cm)
Growth hormone deficiency	No GH treatment	£2,211	16.8					
	GH treatment	£38,031[b.]	18.4	£35,820[b.]	1.54	£23,196[b].	12.80	£2,798[b]
Turner syndrome	No GH treatment	£1,965	15.9					
	GH treatment	£62,752[b].	17.4	£60,787[b].	1.54	£39,460[b].	9.30	£6,536[b]
Prader-Willi syndrome	No GH treatment	£2,646	17.6					
	GH treatment	£67,794[b].	18.1	65,148[b].	0.48	£135,311[b]	11.10	£5,869[b].
Chronic renal insufficiency	No GH treatment	£1,876	11.6					
	GH treatment	£35,877[b].	12.4	34,001[b].	0.87	£39,273[b]	9.20	£3,696[b]
Small for gestational age	No GH treatment	£2,432	17.1					
	GH treatment	34,431[b].	18.1	31,999[b]	0.97	£33,079[b]	3.30	£9,697[b]
SHOX-Deficiency	No GH treatment	£2,646	16.8					
	GH treatment	£53,434[b].	18.1	£50,788[b].	1.25	£40,531[b]	6.30	£8,062[b]

GH, growth hormone; ICER, incremental cost effectiveness ratio; Inc, incremental; QALY, quality adjusted life year.

[b]. taken from table A2 on page 2 of the addendum to the assessment report

Table 14 Cost-effectiveness results for continuation of growth hormone treatment into adulthood for people with growth hormone deficiency

		Costs (£)	QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	cm gain	ICER (£/cm)
Growth hormone deficiency continuers	No GH treatment	£2,211	16.8					
	GH treatment	£45,826[b]	18.4	£43,615[b]	1.54	£28,244[b]	12.80	£3,407[b]

GH, growth hormone; ICER, incremental cost effectiveness ratio; Inc, incremental; QALY, quality adjusted life year.

[b]. taken from table A2 on page 2 of the addendum to the assessment report

Sensitivity analyses

The Assessment Group undertook one-way sensitivity analysis for Turner syndrome, Prader-Willi syndrome, CRI, small for gestational age and *SHOX* deficiency using the KIGS database to estimate clinical effect rather than clinical studies. Results were of a similar magnitude to the base case with the exception of the analyses for small for gestational age where the cost per QALY gained (£18,980) was much lowers because the incremental clinical height gain was lower in the RCT than the KIGS database. See table A4 on page 3 of the addendum to the assessment report.

The Assessment Group stated that the discount rates used for the analyses had a large effect on the results. Using discount rates used in the model for NICE technology appraisal guidance 42, that is costs 6% and benefits 1.5%, GH treatment was more cost effective. For all conditions, except Prader–Willi syndrome, the costs per QALY gained were less than £30,000 (see table A5 on page 3 of the addendum to the assessment report).

The Assessment Group stated that for all conditions, the model results were most sensitive to treatment start age and length, adherence and utility gain. The Assessment Group provides the results of the deterministic sensitivity analyses for the most influential parameters for each condition in tables A6–A11 in the addendum to the assessment report.

The Assessment Group also presented a scenario analysis for Prader–Willi syndrome that included a life-long improvement of body composition of 1.8 kg/m^2 BMI and an associated additional utility of 0.031. Under these assumptions, the cost-effectiveness estimates for Prader–Willi syndrome were reduced to £54,800, per QALY gained (see page 6 of the addendum to the assessment report).

A probabilistic sensitivity analysis undertaken for each of the conditions estimated that the probability of cost effectiveness at willingness to pay thresholds of £20,000, £30,000 and £50,000 per QALY gained respectively was 15%, 88% and 100% for GH deficiency, 0%, 12% and 68% for Turner syndrome, 0%, 0% and 2% for Prader–Willi syndrome, 1%, 11% and 70% for

CRI, 2%, 28% and 86% for small for gestational age, and 3%, 15% and 63% for *SHOX* deficiency, respectively. Further details of the probabilistic sensitivity analyses are provided on pages 122–128 of the assessment report.

3.2.5 Comparison of the Assessment Group's model, the manufacturers' core model and the model for NICE technology appraisal guidance 42

Tables 15–20 illustrate the differences in cost-effectiveness estimates for the three different models: the core model submitted by the five collaborating manufacturers (results from the Pfizer submission for GH deficiency, Turner syndrome, Prader–Willi syndrome, CRI, small for gestational age, results from the Lilly submission for *SHOX* deficiency); the Assessment Group's model for NICE technology appraisal guidance 42 (referred to as the TA 42 model) and the Assessment Group's model for the current appraisal (referred to as the R42 model).

Table 15 Comparison of base-case results for growth hormone deficiency

	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	Height gain (cm)	Cost per cm gained (£)
Pfizer submission	3.48	61,124	17,552	32.24	1,896
TA 42 model	–	53,373	–	8.85[a]	6,029
R 42 model[b.]	1.54	35,820	23,196	12.80	2,798

[a] Discounted and adjusted for drop-outs

[b.] taken from table A2 on page 2 of the addendum to the assessment report

ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Table 16 Comparison of base-case results for Turner syndrome

	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	Height gain (cm)	Cost per cm gained (£)
Pfizer submission	2.83	83,078	29,757	7.95	10,576
TA 42 model	-	61,770	-	3.90[a]	15,997
R 42 model[b]	1.54	60,787	39,460	9.30	6,536

[a] Discounted and adjusted for drop-outs

[b]. from table A2 on page 2 of the addendum to the assessment report

ICER, incremental cost effectiveness ratio**;** QALY**,** quality adjusted life year**.**

Table 17 Comparison of base-case results for Prader–Willi syndrome

	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	Height gain (cm)	Cost per cm gained
Pfizer submission	2.3	74,849	32,540	25.59	2,925
TA 42 model	–	56,663	–	1.36[ab]	40,815
R 42 model[c]	0.48	65,148	135,311	11.10	5,869

[a] Discounted and adjusted for drop-outs

[b] Height gain expressed in terms of height SDS gained

[c] from table A2 on page 2 of the addendum to the assessment report

ICER, incremental cost effectiveness ratio; QALY**,** quality adjusted life year.

Table 18 Comparison of base-case results for CRI

	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	Height gain (cm)	Cost per cm gained
Pfizer submission	2.53	40,325	15,962	4.48	9,001
TA 42 model	–	54,009	–	7.29[a]	7,403
R 42 model[b]	0.87	34,001	39,273	9.20	3,696

[a] Discounted and adjusted for drop-outs

[b] from table A2 on page 2 of the addendum to the assessment report

ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Table 19 Comparison of base-case results for children born small for gestational age

	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	Height gain (cm)	Cost per cm gained
Pfizer submission	2.98	54,088	18,167	21.92	2,467
TA 42 model	–	–	–	–	–
R 42 model[a]	0.97	31,999	33,079	3.30	9,697

[a] from table A2 on page 2 of the addendum to the assessment report

ICER, incremental cost effectiveness ratio**;** QALY**,** quality adjusted life year**.**

Table 20 Comparison of base-case results for *SHOX* deficiency

	Incremental QALYs	Incremental costs (£)	ICER (£/QALY)	Height gain (cm)	Cost per cm gained
Lilly submission	2.83	65,654	23,237	7.95	8,258
TA 42 model	–	–	–	–	–
R 42 model[a]	1.25	50,788	40,531	6.3	8,062

[a] from table A2 on page 2 of the addendum to the assessment report

QALY**,** quality adjusted life year.

The Assessment Group stated that in general the results presented in terms of height gain were more favourable in the current Assessment Group's analyses compared with those from the model used in NICE technology appraisal guidance 42. This was because of higher estimates in height gain and lower incremental costs.

The incremental costs reported were generally considered by the Assessment Group to be consistent between the three models, with slight variations resulting from different dose, cost and treatment start age, and duration. As the incremental costs consisted primarily of the GH drug costs, any differences in other costs had little effect on the model results.

The Assessment Group and the manufacturers' model used different sources for the clinical effect of GH. The Assessment Group used data from studies for all conditions except GH deficiency, for which data were obtained from the KIGS database. However, the manufacturers' model used data from the KIGS database for all conditions. The Assessment Group undertook sensitivity analysis using the KIGS database for estimate of clinical effect. The Assessment Group reported that the results from the sensitivity analysis were of a similar magnitude to their own base case.

The Assessment Group stated that the choice of utility values was the key issue in explaining the differences in the Assessment Group's and manufacturers' cost-effectiveness results. The Assessment Group and manufacturers had chosen utility estimates from the same study. However, the manufacturers had taken values from the relationship between EQ–5D and height while the Assessment Group had taken them from the regression analysis.

4 Issues for consideration

4.1 The cost effectiveness estimates presented by the Assessment Group are sensitive to the clinical effect of additional height gained as a result of treatment. The height gains in the Assessment Group's ' economic model for Turner syndrome, Prader–Willi

syndrome, CRI, children born small for gestational age and *SHOX* deficiency were derived from studies identified for their review of clinical effectiveness. However, the Assessment group highlighted that these studies were of generally poor quality and of short duration. The uncertainty in the size of clinical effect arising from the limitations of the studies was addressed in sensitivity analysis undertaken by the Assessment Group. The Assessment Group used clinical treatment effect from the KIGS database where the results were similar to the Assessment Groups base-case analyses with the exception of children born small for gestational age.

4.2 The manufacturer and the Assessment Group used the study by Christensen et al. (2007) as the source of utility data for their health economic models but different approaches in using these utility values. The manufacturers performed a linear interpolation of the utility scores to determine a utility value for each 0.01 increment in height SDS. The Assessment Group used the OLS linear regressions in the study to control for confounding factors including age, gender, weight, social class and long-standing illness. The approach taken by the Assessment Group results in a lower QALY gains across all indications compared with the manufacturers' approach. Which approach for obtaining utility values does the Committee consider the most appropriate for use in the economic modelling?

4.3 There is evidence to suggest that there are additional health benefits associated with GH treatment such as improvement in body composition, lipid profiles, bone mineral density, behaviour, total IQ and self-perception. However the Assessment Group highlighted that there is considerable difficulty in estimating the size of such benefits and extrapolating short-term treatment in childhood to lifelong benefit.

5 Ongoing research

5.1 Study NCT00190658 aims to compare the mean first year growth velocity of somatropin-treated prepubertal children with *SHOX* deficiency with the growth velocity of a control group of untreated prepubertal children with *SHOX* deficiency. Both groups will be compared with a somatropin-treated group of girls with Turner syndrome. Sponsor: Lilly. Estimated end date: December 2010.

5.2 Study NCT00625872 focuses on the effect of a 1-year somatropin treatment (0.035 mg/kg/day or 0.067 mg/kg/day) in short children born small for gestational age on neuromuscular function and cognitive performance. Height gain and growth velocity are included as secondary outcome measures. Inclusion criteria are birth length SDS and/or birth weight SDS adjusted to gestational age less than −2.0, current height SDS less than −2.5 and parental adjusted height SDS below −1, growth velocity SDS less than 0 during the year before inclusion. Sponsor: Pfizer; end date: not reported.

5.3 There is a cohort study examining health-related quality of life in families of children prescribed GH treatment for idiopathic GH deficiency, acquired GH deficiency and Turner syndrome. Inclusion criteria for the treatment group and control groups are children with idiopathic or acquired GH deficiency or Turner syndrome, who are about to start GH treatment and children whose height is on or below the 2nd percentile who are not treated with GH respectively. In September 2009, one of the investigators informed NICE that results were not expected until the end of 2010.

6 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by Southampton Health Technology Assessment Group:

- Takeda A, Cooper K, Bird A et al, Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation, September 2009.

B Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- Eli Lilly & Co Ltd
- Merck Serono
- Novo Nordisk Ltd
- Pfizer Limited
- Sandoz Limited

II Professional/specialist, patient/carer and other groups:

- British Society of Paediatric Endocrinology and Diabetes
- Growth Foundation
- Pituitary Foundation
- Royal College of Nursing
- Royal college of Paediatrics and Child Health
- Royal college of Pathologists
- Royal college of Physicians
- Turner Syndrome Support Society

Appendix B: Guidance on the use of human growth hormone (somatropin) in children with growth failure. NICE technology appraisal 42 (2002)

1.1 Recombinant human growth hormone (somatropin) treatment is recommended for children with proven clinical diagnosis of growth hormone (GH) deficiency supported by appropriate auxological, biochemical and radiological investigations.

1.2 GH treatment is recommended for children with Turner syndrome (TS). The following issues should be taken into consideration in order to maximise the benefit from this treatment:

- diagnosis and treatment at earliest age possible
- appropriate timing and use of oestrogen therapy.

1.3 GH treatment is recommended for pre-pubertal children with chronic renal insufficiency (CRI) providing:

- nutritional status has been optimised
- metabolic abnormalities have been optimised
- steroid therapy has been reduced to minimum.

1.4 GH treatment is recommended for children with Prader-Willi syndrome.

1.5 GH treatment should, in all circumstances, be initiated and monitored by a paediatrician with special expertise in the management of children with GH disorder. Continuation of treatment can be maintained under an agreed shared-care protocol with a general practitioner.

1.6 GH treatment should be re-evaluated and normally discontinued if

there is a poor response to treatment, defined as an increase in growth velocity of less than 50% from baseline, in the first year of therapy. Ongoing response should be evaluated against expected growth based

on standard growth charts. Therapy should normally be stopped when final height is approached and growth velocity is less than 2 cm total growth in 1 year. Persistent and uncorrectable problems with adherence to treatment should also be taken into account as part of re-evaluation of treatment. In Prader-Willi syndrome evaluation of response to therapy should also consider body composition.

1.7 After attainment of final height, GH therapy will normally be discontinued, but it should not be discontinued by default. The decision to stop treatment should either be made by a paediatrician with special expertise in the management of children with GH disorders in consultation with patient and carers, or therapy should be continued until re-evaluation by an adult endocrinologist has been undertaken. The transition to adult care for people with GH disorders will require a close collaboration between the responsible clinicians.

1.8 In children with CRI, GH treatment should be stopped after renal transplantation. It should not normally be re-started until at least 1 year after renal transplantation to allow time to ascertain whether catch-up growth will occur.

1.9 The use of GH therapy in children with idiopathic short stature is currently not licensed, and therefore it was not considered as part of this appraisal