NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Human growth hormone (somatropin) for the treatment of growth failure in children (review of NICE technology appraisal guidance 42)

1 Guidance

1.1 Somatropin (recombinant human growth hormone) is recommended as a treatment option for children with growth failure associated with any of the following conditions:

- growth hormone deficiency
- Turner syndrome
- Prader–Willi syndrome
- chronic renal insufficiency
- born small for gestational age with subsequent growth failure at 4 years of age or later
- short stature homeobox-containing gene (*SHOX*) deficiency.

1.2 Treatment with somatropin should always be initiated and monitored by a paediatrician with specialist expertise in managing growth hormone disorders in children. The choice of product should be made on an individual basis after informed discussion between the responsible clinician and the patient and/or their carer about the advantages and disadvantages of the products available, taking into consideration therapeutic need and the likelihood of adherence to treatment. When more than one product is suitable, the least costly product should be chosen.

1.3 Treatment with somatropin should be discontinued if any of the following apply:

- growth velocity increases less than 50% from baseline in the first year of treatment
- final height is approached and growth velocity is less than 2 cm total growth in 1 year
- there are insurmountable problems with adherence
- final height is attained.

In Prader–Willi syndrome evaluation of response to therapy should also consider body composition.

Treatment should not be discontinued by default. The decision to stop treatment should be made in consultation with the patient and/or carers either by:

- a paediatrician with specialist expertise in managing growth hormone disorders in children, or
- an adult endocrinologist, if care of the patient has been transferred from paediatric to adult services.

2 Clinical need and practice

2.1 Human growth hormone is produced by the anterior pituitary gland. The synthetic form is called somatropin (recombinant human growth hormone). Human growth hormone is essential for normal growth in children. It increases growth by a direct action on the growth plates and by production of insulin-like growth factors (especially IGF-1), mainly in the liver. Human growth hormone also has important effects on the metabolism of proteins, lipids and carbohydrates, not only during childhood, but also throughout adult life. Growth failure in children can be a result of growth hormone deficiency, but also occurs in children with Turner syndrome, chronic renal insufficiency (CRI), short stature homeobox-containing gene (*SHOX*) deficiency, and in children born small for gestational age.

2.2 Growth hormone deficiency occurs when the pituitary gland does not produce enough human growth hormone, which is the most common endocrine cause of short stature. Growth hormone deficiency may occur as an isolated hormonal deficiency or in combination with deficiencies in several pituitary hormones arising from hypopituitarism, tumours in the central nervous system, cranial irradiation or other physiological causes. The prevalence of growth hormone deficiency is estimated to be between 1 in 3500 and 1 in 4000 children. In about half of the children with growth hormone deficiency (50%), the cause is unknown (idiopathic growth hormone deficiency).

2.3 Turner syndrome is a chromosomal disorder characterised by the complete or partial lack of one X chromosome in girls. The two most common clinical features are short stature and ovarian failure. Girls with Turner syndrome do not have a deficiency in human growth hormone, although they may have a relative lack of sensitivity to human growth hormone because of haploinsufficiency of the short stature homeobox-containing gene. Not all girls with Turner syndrome need treatment with somatropin. Turner syndrome occurs in between 1 in 1500 and 1 in 2500 live female births. If untreated, girls with Turner syndrome have a final adult height of 136–147 cm. Adult women with Turner syndrome are on average 20 cm shorter than other adult women.

2.4 Prader–Willi syndrome is a genetic disorder caused by an abnormality of chromosome 15. Common clinical characteristics include hypogonadism, short stature, hypotonia, dysmorphic features, hypoventilation, changes in body composition, obesity and obesity-related diseases, and behavioural problems. Prader–Willi syndrome occurs in between 1 in 15,000 and 1 in 25,000 live births. Men with Prader–Willi syndrome have a final adult height of about 154 cm; women have a final adult height of 145–159 cm.

2.5 Chronic renal insufficiency (CRI), which may include end-stage renal disease, 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 associated with CRI usually begins when the glomerular filtration rate falls to 50% of normal. Not all people with CRI in childhood will be shorter than average; figures from the UK Renal Registry indicate that 29% of children who undergo renal transplantation and 41% of children on dialysis are below the 2nd percentile for height within their first year and remain so throughout childhood because of more pronounced deceleration in height velocity. Children with congenital disorders leading to CRI (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 so throughout childhood.

2.6 Various thresholds for height and weight at birth are used to define 'small for gestational age', the three most commonly used being:

- a height at birth that is 2 standard deviations or more below the population average, or
- a weight at birth that is 2 standard deviations or more below the population average, or
- a weight at birth below the 10th percentile.

In addition to accurate measurements of a newborn's weight, length and head circumference, the diagnosis of small for gestational age requires accurate assessment of gestational age and valid data from a reference population. The international consensus definition of 'small for gestational age' is a length or weight at birth that is 2 standard deviations below (< -2 SD) the population average for birth or weight. The licensed indication for somatropin is for growth disturbance (current height standard

deviation score [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 failed to show catch-up growth (height velocity SDS less than 0 during the past year) by 4 years of age or later. Children classified as born small for gestational age may have concurrent diagnoses such as familial short stature, Turner syndrome, or growth hormone deficiency. Approximately 10% of children born small for gestational age do not reach the normal height range. Those whose growth has not caught up by 4 years of age are candidates for treatment with growth hormone.

2.7 The short stature homeobox-containing gene *(SHOX)* is located on the distal ends of X and Y chromosomes and plays a role in long bone growth. Normal growth requires two functional copies of the gene. Consequently, growth impairment can occur if one copy of the *SHOX* gene has been inactivated by mutation or deleted (haploinsufficiency). *SHOX* deficiency can cause short stature in people with conditions such as Turner syndrome, Leri–Weil syndrome and dyschondrosteosis. Based on a small study (26 people with *SHOX* haploinsufficiency compared with 45 of their unaffected relatives), children with *SHOX* haploinsufficiency were 3.8 cm shorter (2.1 standard deviations shorter) than their unaffected relatives and this difference persisted throughout their childhood.

2.8 Somatropin (recombinant human growth hormone) is currently the only active treatment option for growth failure in children with growth hormone deficiency, Turner syndrome, CRI, Prader–Willi syndrome, in short children born small for gestational age and in children with *SHOX* deficiency. The place of somatropin in the treatment pathway depends on the child's particular condition, his or her age at diagnosis and the licensed indications of the seven

somatropin preparations that are available for use in UK practice. For girls with Turner syndrome, oxandrolone, an anabolic steroid, may be added to growth hormone treatment. In the UK, conservative strategies for the management of growth failure in children with CRI include advice on diet and nutritional supplementation.

3 The technologies

3.1 In the UK, seven preparations of somatropin are available: Genotropin, Pfizer; Humatrope, Lilly; Norditropin, Novo Nordisk; NutropinAq, Ipsen; Omnitrope, Sandoz; Saizen, Merck Serono; Zomacton, Ferring. Each product is produced by recombinant DNA technology and has a sequence identical to that of human growth hormone produced by the pituitary gland. The licensed indications are as follows (for the different products the wording may differ):

- growth disturbance in children due to insufficient secretion of growth hormone (growth hormone deficiency).
- growth failure in girls associated with gonadal dysgenesis (Turner syndrome).
- growth retardation in prepubertal children associated with chronic renal insufficiency (CRI).
- improvement of growth and body composition in children with Prader–Willi syndrome. The diagnosis of Prader–Willi syndrome should be confirmed by appropriate genetic testing.
- growth disturbance (current height standard deviation score [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 failed to 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.

3.2 The seven manufacturers have UK marketing authorisations for somatropin for the following indications:

- Lilly (Humatrope): growth hormone deficiency; Turner syndrome; CRI; short children born small for gestational age and *SHOX* deficiency.
- Ferring (Zomacton): growth hormone deficiency and Turner syndrome.
- Ipsen (NutropinAq): growth hormone deficiency; Turner syndrome and CRI.
- Novo Nordisk (Norditropin SimpleXx): growth hormone deficiency; Turner syndrome; CRI and short children born small for gestational age.
- Pfizer (Genotropin): growth hormone deficiency; Turner syndrome; CRI; Prader–Willi syndrome and short children born small for gestational age.

- Sandoz (Omnitrope)[1]: growth hormone deficiency; Turner syndrome; CRI; Prader–Willi syndrome and short children born small for gestational age.

- Merck Serono (Saizen): growth hormone deficiency; Turner syndrome; CRI and short children born small for gestational age.

3.3 The summary of product characteristics for somatropin states that the dosage and the administration of somatropin should be tailored to the needs of each individual child. The dosage varies according to the condition being treated: 23–29 microgram/kg daily or 0.7−1.0 mg/m² daily for growth hormone deficiency; 45−50 microgram/kg daily or 1.4 mg/m² daily for Turner syndrome and CRI; 35 microgram/kg daily or 1.0 mg/m² daily for growth disturbance in children born small for gestational age; 35 microgram/kg daily or 1.0 mg/m² daily (with a maximum of 2.7 mg daily) for Prader–Willi syndrome; and 45–50 microgram/kg daily for *SHOX* deficiency. Somatropin is self-administered or given to the child by an adult, at home, usually as a subcutaneous injection, 6–7 times a week.

3.4 The summary of product characteristics for somatropin states that side effects include headache, visual problems, nausea and vomiting, fluid retention (peripheral oedema), arthralgia, myalgia, carpal tunnel syndrome, paraesthesia, antibody formation, hypothyroidism and reactions at injection site. Paediatricians

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Omnitrope is a 'similar biological medicinal product' or 'biosimilar'. Genotropin is the biological reference medicine for Omnitrope BNF 58 states the following: A similar 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. . Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no important differences between the biosimilar and the biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed.

should pay particular attention when giving somatropin to children with diabetes mellitus or its risk factors, slipped capital epiphyses, idiopathic intracranial hypertension or malignancies. For full details of side effects and contraindications, see the summary of product characteristics.

3.5 The cost of treatment with somatropin depends on the dose, which is determined by the weight or body surface area of the child as well as by the indication for growth hormone treatment. The costs of the different somatropin products (excluding VAT; 'British national formulary' [BNF] edition 58) are: £23.18 per mg for Genotropin, £18.00 per mg for Humatrope, £21.39 per mg for Norditropin, £20.70 per mg for Nutropin, £18.26 per mg per mg for Omnitrope, £23.18 per mg for Saizen and £19.92 per mg for Zomacton. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

Published reviews

4.1.1 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 more recent systematic review of growth hormone in Turner syndrome undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2007.

4.1.2 The systematic review for NICE technology appraisal guidance 42 included randomised controlled trials (RCTs) comparing somatropin with placebo or no treatment in children with growth hormone

deficiency, Turner syndrome, CRI and Prader–Willi syndrome. Non-randomised and observational studies were included when RCTs lacked data on change to final height. The Assessment Group concluded that although the quality of evidence was variable, there was evidence that treatment with somatropin could increase short-term growth and improve final height. Results suggested that effects of somatropin on short-term growth velocity (1 year) ranged from no improvement to approximately 1 standard deviation above the normal growth velocity for children of the same age. Gains in final height for children treated with somatropin compared with untreated children ranged from approximately 3 to 11 cm (for growth hormone deficiency 8–11 cm, for Turner syndrome 5 cm, for CRI 3–9 cm, for Prader–Willi syndrome 10–11 cm).

4.1.3 The systematic review undertaken by the CADTH included 19 RCTs or observational studies that compared somatropin with placebo or no treatment in girls with Turner syndrome. All studies included measurements of growth (final height, interim height, growth velocity), documentation of adverse events and measures of quality of life. The review found that growth was accelerated and height increased in girls taking somatropin for Turner syndrome. No serious adverse events were reported.

Assessment Group's systematic review

4.1.4 The Assessment Group conducted a systematic review for RCTs of somatropin in children with growth disturbance, according to the marketing authorisations for somatropin (see sections 3.1 and 3.2). The Assessment Group could not identify any RCTs meeting the inclusion criteria for children born small for gestational age. The Assessment Group included studies that compared the effectiveness of somatropin with management strategies that did not include treatment with somatropin.

4.1.5 The Assessment Group identified a total of 28 RCTs from 34 publications. The Assessment Group excluded a number of studies that had been included in the review for NICE technology appraisal guidance 42. This was partly because the Assessment Group included only RCTs in its review whereas the review for NICE technology appraisal guidance 42 had included non-randomised studies. The Assessment Group also excluded three RCTs (two for Turner syndrome and one for Prader–Willi syndrome) that were included in the review for the previous appraisal. One of the excluded studies used methionyl growth hormone rather than somatropin and two others reported outcomes not included in the Assessment Group's inclusion criteria.

4.1.6 The studies included in the Assessment Group's systematic review reported at least one of the following outcomes: final height; height standard deviation score (height SDS); growth velocity; growth velocity SDS; body composition; biochemical and metabolic markers; and adverse events. None of the studies reported health-related quality of life. The Assessment Group did not perform a meta-analysis because of heterogeneity in study design and participants. For conciseness, only growth outcomes and adverse events are presented here for growth hormone deficiency, Turner syndrome, CRI, small for gestational age and *SHOX* deficiency. For Prader–Willi syndrome, a summary of outcomes for body composition is also presented.

Growth hormone deficiency

4.1.7 The Assessment Group identified one RCT comparing treatment with somatropin against no treatment in children with growth hormone deficiency. Children in the treated group (n = 9) grew an average of 2.7 cm per year faster than those receiving no treatment (n = 10) in the 12 months of the study. The difference between the groups was statistically significant ($p < 0.05$). Children in the

treated group had a statistically significantly higher height SDS (−2.3 ± 0.45) than children in the untreated group (−2.8 ± 0.45; $p < 0.05$). The study did not report adverse events. The study was unblinded and did not report an intention-to-treat analysis. The Assessment Group considered the reporting and the methodological quality of the study to be mixed.

Turner syndrome

4.1.8 The Assessment Group identified six RCTs of somatropin for the treatment of growth restriction in girls with Turner syndrome. All six studies were published after the publication of NICE technology appraisal guidance 42. Two of the included studies (of 9 and 12 girls respectively) had a crossover design that compared somatropin with placebo. Of the four remaining studies, two (of 89 and 154 girls) compared somatropin with no treatment, one (of 58 girls) compared somatropin with low-dose oestrogen, and one (of 232 girls) compared somatropin with placebo. The Assessment Group considered the reporting and methodological quality of the studies to be generally poor.

4.1.9 The two studies that reported final height as an outcome found a statistically significant difference in height between the treated and untreated groups at the end of the studies ($p < 0.001$). In one of the studies, girls grew an average of 9.3 cm more from baseline than those in the untreated group. In the other study, which recruited younger girls, the difference was 7.6 cm. Both studies reported statistically significantly higher height SDS in girls treated with somatropin than in untreated girls. Height velocity was statistically significantly greater in the treated groups in the three studies reporting height velocity as an outcome. One study reported height velocity at the end of the first and second years; height velocity was greater in the first year and fell in the second year in both treatment groups.

4.1.10 Adverse events were reported in four studies. One study reported higher rates of adverse events in the treated group, one reported similar levels across groups, and one reported a significantly more frequent occurrence or worsening of ear infections. One study reported four withdrawals because of problems with adherence.

Prader–Willi syndrome

4.1.11 The Assessment Group identified eight RCTs from 13 publications that investigated somatropin for the treatment of Prader–Willi syndrome and that met the inclusion criteria for this review. Three had been considered previously for NICE technology appraisal guidance 42 and five were new studies published after the guidance. Seven of the RCTs compared somatropin at a dosage of 1 mg/m^2 body surface area per day with no treatment for 1 year (six studies) or 2 years (two studies, including one which treated infants for I year only). One study (of 14 children) was a crossover RCT that compared somatropin at a dosage of 43 microgram/kg body weight per day with placebo over 6 months in each treatment group. The doses used in the included studies reflect the marketing authorisations for the different preparations of somatropin. The Assessment Group considered the reporting of the studies to be generally poor.

4.1.12 In the only study that reported changes in height, infants who received somatropin for 1 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 at end of treatment between participants randomised to treatment and those randomised to no treatment. A difference of 1 SDS (favouring somatropin treatment) was reported in one study at 1 year ($p < 0.01$) and more than 2 SDS in the other at 2 years ($p < 0.0001$).

4.1.13 Three studies reported growth velocity as an outcome. Children treated with somatropin grew 3 cm per year more than untreated

children in one study and 5 cm per year more in another. Another study reported a positive growth velocity SDS for children treated with somatropin and a negative growth velocity SDS for untreated children (5.5 versus −2.3). The differences between groups were statistically significant in all three studies.

4.1.14 Four studies reported a statistically significantly lower percentage of body fat in children treated with somatropin compared with children who received no treatment or who received placebo. In one study, the mean percentage of body fat was 10% lower for children treated with somatropin than for untreated children ($p = 0.03$). In this study children treated with somatropin experienced approximately a 5% reduction in body fat, compared with an average 4% increase in body fat in the untreated children ($p = 0.001$). Two other two studies reported that treated children had approximately 4% or 7% less body fat than those in the comparator group. The fourth study did not report the percentage body fat for infants, but did report this outcome for children over 4 years. Children who received somatropin for a year had a median percentage body fat SDS of 1.5, compared with 2.3 in the control group ($p < 0.001$). After 2 years of treatment, the SDS values were 1.9 versus 2.4 for the treated and untreated groups respectively ($p < 0.001$).

4.1.15 Four studies reported that children treated with somatropin had a statistically significantly higher lean body mass or a larger increase in lean body mass than untreated children. In one study, the lean body mass of children treated with somatropin increased by 1.8 kg more than in the untreated group (3.6 versus1.8 kg, $p < 0.001$). In two other studies children treated with somatropin had approximately 2 kg or 4 kg more lean body mass than untreated children ($p < 0.05$ and $p < 0.01$ respectively). One study reported that change in trunk lean body mass was statistically significantly

greater for treated than for untreated infants (1.7 versus 0.7 respectively). For children (but not infants), the study reported SDS for lean body mass adjusted for age and height, as well as change in trunk lean body mass. There was a statistically significant difference for all of these outcomes between treated and untreated children after both 1 and 2 years of treatment.

4.1.16 Six studies reported body mass index (BMI), but results were mixed. Some studies showed higher values of BMI in treated groups, and others showed no difference. One study reported a BMI of 16.1 after 1 year for children treated with somatropin compared with 18.5 for untreated children ($p < 0.05$); results were similar after 2 years. A small crossover RCT also reported a statistically significant difference in BMI for treated children compared with those receiving placebo (31.2 compared with 32.8, $p < 0.05$). In contrast, two studies found no statistically significant difference in BMI for children treated with somatropin and untreated children. Neither of the remaining two studies that reported BMI gave a value for between-group statistical significance, but both treated and untreated children had similar values of BMI.

4.1.17 No serious adverse events were reported in the five studies that presented data.

Chronic renal insufficiency

4.1.18 The Assessment Group identified six RCTs that investigated somatropin treatment in children with CRI. Four had been considered for NICE technology appraisal guidance 42 (TA 42) and two were new studies published after TA 42. Two RCTs were crossover studies and four were parallel-group studies. Three of the four parallel-group RCTs (of 23, 69 and 203 children) had an open-label design, with the comparator groups receiving no treatment. One trial (of 125 children) was placebo controlled. The two crossover studies (of 20 and 11 children) had placebo and

treatment phases. Three of the studies investigated somatropin treatment in children who had received a kidney transplant and the other three studied children who had CRI but no renal transplant. The Assessment Group considered the reporting of the trials to be generally poor.

4.1.19 One study reported gain in absolute height and found that after 1 year children treated with somatropin grew an average of 3.6 cm more than those who were untreated (height gain 9.1 cm versus 5.5 cm, $p < 0.0001$). Two studies reported that height SDS showed statistically significant greater growth in children treated with somatropin than those who were untreated. Five studies reported that change in growth velocity or growth velocity SDS was statistically significantly greater for children who received somatropin treatment than for those children who did not. The between-group differences in growth velocity ranged from 3.2 cm per year to 4.2 cm per year in the parallel-group trials.

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

Children born small for gestational age

4.1.21 The Assessment Group did not identify any RCTs that met the criteria for use of somatropin in children as prescribed in the licence for growth hormone in children born small for gestational age (see section 3.1). Therefore, the Assessment Group amended the criteria for the review to the following: growth disturbance (current height SDS < -2.5, no reference to parental height) in children with a birth weight and/or length < -2 SD and no catch-up growth (no stated criteria) by the age of 3 years.

4.1.22 The Assessment Group identified six RCTs that met the amended inclusion criteria for the review (of 13, 40, 40, 54, 151 and 168 children). All studies compared somatropin with no treatment.

Duration of treatment was comparable across five of the six studies. In the sixth study children received treatment for 2 years, but only the first year allowed a randomised comparison between somatropin and no treatment. Only one study included a treatment arm with the licensed dose of somatropin; the other studies all used approximately two to three times the dose licensed for use in the UK. The Assessment Group considered the studies to be generally of poor methodological quality.

4.1.23 One study reported a total gain in adult height of approximately 4 cm in people who had received somatropin. The difference between groups was statistically significant ($p < 0.005$). Adult height SDS was also statistically significantly higher in people who had received somatropin. However, the study used a dose approximately twice that licensed for use in the UK, and the study included children with a mean age of 12.7 years at start of treatment. The Assessment Group cautioned that generalisability of the results may be limited. One study reported that children who received somatropin at a dosage of 33 microgram/kg body weight per day (licensed dosage 35 microgram/kg per day) gained an additional 3.3 cm in height compared with untreated children, and those who received a higher dose of 100 microgram/kg per day gained 6.5 cm after 1 year's treatment. Height SDS was statistically significantly higher in children treated with somatropin in two studies, and higher (but with no reported p value) in two others. Treatment was associated with a greater growth velocity at the end of year 2 in the two studies that reported this outcome, but the difference was reported to be statistically significant in only one study ($p < 0.001$).

4.1.24 Four studies reported limited information on adverse events. One study reported two adverse events in treated children. A second reported only that there were 'no noteworthy' adverse events. A

third study reported four serious adverse events that were not linked to the study drug. In the remaining study, three adverse events were linked to somatropin and resolved or stabilised after stopping treatment.

SHOX deficiency

4.1.25 The Assessment Group identified one study of children with *SHOX* deficiency. The 2-year multicentre RCT compared a daily injection of 50 micrograms of somatropin with no treatment in 52 prepubertal 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 calculate dosage by body weight and to know whether or not the study used a licensed dose of somatropin. The unblinded study did not report an intention-to-treat analysis.

4.1.26 By the end of the second year, children treated with somatropin had gained statistically significantly more height and had higher values of height SDS than those in the control group. Treatment with somatropin 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).

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

Summary of clinical effectiveness

4.1.28 The identified studies reported statistically significantly greater values for height SDS for children treated with somatropin than for untreated children for all indications. For children with Prader–Willi syndrome, treatment with somatropin was also associated with statistically significant changes in measures of body composition. None of the studies reported data on health-related quality of life and the reporting of adverse events was limited.

Health-related quality of life

4.1.29 Because there were no data on health-related quality of life in studies included in the systematic reviews, the Assessment Group undertook a literature search to identify publications reporting utility values in relation to height. One study was identified that provided estimates for utility based on the EuroQoL (EQ–5D) for different height SDS from the Health Survey for England for an adult general population (14,416 adults). Inter-relationships using linear regression between height SDS and quality of life were assessed for height SDS alone, and also controlling for age, body weight, sex, social class and long-standing illness. The study identified a positive correlation between an increase in height and a participant's EQ–5D score. Mean EQ–5D scores were lower in people who were shorter than in people who were taller, as well as lower than the overall population mean. The study categorised participants into three groups: people shorter than −2.0 height SDS, people with a height SDS between −2.0 and 0.0, and people with average or above average height. The EQ–5D scores for these groups were statistically significantly different from each other ($p < 0.05$). Adjusted for potential confounders, increasing values of height were associated with greater gains in quality of life in shorter people compared with taller people. An increase in height SDS of 1.0 was associated with an increase in EQ–5D score in the shortest group of 0.061, an increase of 0.010 in the middle group, and an increase of 0.002 in the group with average or above average height.

4.1.30 The Assessment Group concluded that there was likely to be a gain in utility associated with height gain for people receiving treatment with somatropin. The Assessment Group acknowledged that the available evidence for utility excludes potential benefits of treatment with somatropin which include change in body composition and lipid profiles.

4.2 Cost effectiveness

Published studies

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

4.2.2 The Assessment Group identified two North American economic evaluations for somatropin treatment, which had been published since the economic evaluation for NICE technology appraisal guidance 42: one for children with Turner syndrome (by the CADTH) and one for children with growth hormone deficiency. The economic evaluation of somatropin treatment 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 somatropin treatment in children with growth hormone deficiency estimated ICERs of US$36,995 per QALY for the 5- to 16-year-old cohort and US$42,556 per QALY gained for the 3- to 18-year-old cohort.

4.2.3 The Assessment Group stated that the two different estimates of cost effectiveness were largely because of differences in the choice of estimates of utility (the utility increment associated with growth hormone treatment ranged from 0.040 to 0.189) and difference in assumptions on effectiveness. The Assessment Group considered the economic evaluation undertaken by the CADTH to be of higher quality, and the parameter estimates more appropriate, because

the group established the effectiveness of the treatment from a systematic review. The Assessment Group concluded that the previous economic evaluations lacked reliable estimates of gains in utility associated with treatment with somatropin, and that the results should be treated with caution.

Manufacturers' economic model

4.2.4 Six of the seven manufacturers submitted cost-effectiveness evidence. The Assessment Group stated that the cost-effectiveness evidence submitted by Sandoz, a cost-minimisation analysis using Genotropin as a comparator, did not comply with the requirements for the NICE reference case The submission contained a comparison of the annual cost of treatment with Omnitrope and with Genotropin in children with growth hormone deficiency and Turner syndrome.

4.2.5 Five of the six manufacturers (Lilly, Ipsen, Novo Nordisk, Pfizer and Merck Serono) collaborated to develop a de novo core economic model to estimate the cost effectiveness of somatropin treatment in children with growth hormone deficiency, Turner syndrome, Prader–Willi syndrome, CRI or children born small for gestational age. The model was developed by Pfizer, but each of the collaborating manufacturers presented the model with minor modifications (for example, changes in the unit price of somatropin). Merck Serono's economic model included a waste elimination model to examine the differences in costs likely to be associated with using the Easypod device rather than other delivery systems. Novo Nordisk constructed a decision tree model to assess the cost effectiveness of somatropin treatment for the four licensed indications for Norditropin (that is, growth hormone deficiency, Turner syndrome, CRI and being born small for gestational age). The assumptions underpinning the model, source

of clinical effect, and utility data were identical to those in the core economic model.

Manufacturers' core economic model

4.2.6 The manufacturers developed a Markov cohort model for the economic evaluation containing two health states: 'alive' and 'dead'. The manufacturers estimated the transition probabilities between states using UK-specific mortality rates observed in the general population. The economic model considered a 1-year cycle length. Two alternative model structures were also presented. One allowed for a reduction in the risk of osteoporosis in children with growth hormone deficiency treated with somatropin and assumed that some children with growth hormone deficiency would continue treatment until they reached 25 years of age. A second model incorporated a cost-effectiveness analysis of somatropin in Prader–Willi syndrome. This model assumed that people with Prader–Willi syndrome and diabetes would have a 10% lower quality of life than those without diabetes.

4.2.7 The manufacturers assumed no difference in life expectancy between the general population and those with growth hormone deficiency, Turner syndrome, Prader–Willi, CRI, being born small for gestational age or *SHOX* deficiency. For Prader–Willi syndrome, the manufacturers assumed that changes in body composition associated with somatropin treatment would result in a reduction in the risk of developing diabetes and death related to diabetes. They assumed that the prevalence of diabetes among people with Prader–Willi syndrome would be reduced from 8% to 2%.

4.2.8 The utility values used in the model for children with growth hormone deficiency, Turner syndrome, CRI and children born small for gestational age were taken from the study described in section 4.1.29. The manufacturers assumed that a gain in height was associated with improvement in quality of life, which was assessed

using the EQ–5D utility scale. The values were interpolated from the association between height SDS and EQ–5D score unadjusted for other factors that might be associated with both height and quality of life. The gain in utility value for Prader–Willi syndrome was based on a study of 13 adults with Prader–Willi syndrome who received somatropin for 2 years. The estimate for clinical effectiveness and many of the other parameters used in the model were derived from the Kabi International Growth (KIGS) observational database, a large-scale collaborative database developed by Pfizer to store data on the safety and efficacy of treatment with somatropin. As *SHOX* deficiency is not a licensed indication of Genotropin, it is not included in the KIGS database Therefore the same values were assumed for *SHOX* deficiency as for Turner syndrome.

4.2.9 The costs used in the model were those used in the model for NICE technology appraisal guidance 42 and were adjusted for inflation to current prices. The mean daily per patient cost for each manufacturer's formulation of somatropin was based on the unit costs described in section 3.5.

4.2.10 For comparison with NICE technology appraisal guidance 42, the base-case analyses estimated the incremental cost of somatropin per centimetre of height gained relative to no treatment. Costs ranged from £1699 to £2136 per cm gained for growth hormone deficiency, from £2022 to £2596 per cm gained for growth hormone deficiency with somatropin continued through the transition years from age 18 to 25 years, from £8258 to £10,576 per cm gained for Turner syndrome, from £7048 to £11,345 per cm gained for CRI and from £1932 to £9123 per cm gained for small for gestational age. The base-case analyses for Prader–Willi syndrome and *SHOX* deficiency produced costs per centimetre gained of £2925 and £8258 respectively.

4.2.11 The incremental cost effectiveness ratios (ICERs) for the base case ranged from: £15,730 to £17,522 per QALY gained for growth hormone deficiency; £18,721 to £20,881 per QALY gained for growth hormone deficiency with somatropin continued through the transition years from age 18 to 25; £26,630 to £29,757 per QALY gained for Turner syndrome, £12,498 to £15,962 per QALY gained for CRI and from £14,221 to £18,655 per QALY gained for small for gestational age. The base-case analyses for Prader–Willi syndrome and *SHOX* deficiency produced ICERs of £32,540 and £23,237 per QALY gained respectively.

4.2.12 The ICERs were most sensitive to the choice of utility values, time horizon, discount rates, treatment duration, doses during the transition phase for those with growth hormone deficiency, the proportion of people achieving final height, and drug price.

Assessment Group's model

4.2.13 The Assessment Group developed a state transition Markov model based on the model developed for NICE technology appraisal guidance 42. The modelled health states were 'alive' and 'dead'. The economic model considered a cycle length of 1 year and a life time horizon of 100 years. The mortality rates for the population in England and Wales were applied in each cycle and the rates were adjusted upward using the standard mortality rates for each of the conditions. The Assessment Group presented an additional scenario for growth hormone deficiency in which it assumed that 34% of people with growth hormone deficiency continued treatment until age 25 years at a dosage of 40 microgram/day. The model assumes that this group does not receive additional benefits from somatropin beyond those associated with attaining final height.

4.2.14 The Assessment Group assumed that life expectancy for all conditions considered in this appraisal was lower than for the UK general population. Life expectancy for the UK general population

was assumed to be 75 years for men and 79 years for women. Life expectancy for people with growth hormone deficiency, Prader–Willi syndrome, born small for gestational age and *SHOX* deficiency was assumed to be reduced to 68 years for men and 70 years for women. Life expectancy for women with Turner syndrome was assumed to be 70 years. For men with CRI life expectancy was assumed to be 35 years and 42 years for women with CRI.

4.2.15 Ages at start and end of treatment and duration of treatment for growth hormone deficiency, CRI, Prader–Willi syndrome and small for gestational age were taken from the KIGS database. For *SHOX* deficiency, age at start of treatment was taken from the study described in section 4.1.25. The clinical effectiveness of somatropin was taken from the systematic review (sections 4.1.4 to 4.1.27) and where possible from the best quality RCT with at least 2 years of treatment duration. Data for clinical effectiveness were not available for growth hormone deficiency, so the Assessment Group used data from the KIGS database. For the children born small for gestational age, data were used from a study with 1 year of treatment. In addition, for Turner syndrome, age-specific height SDS data were taken from the KIGS database. For the studies that had not reported height gain in centimetres, the Assessment Group converted height SDS values to centimetres using the height table from the Health Survey for England 2003. The Assessment Group assumed an adherence rate of 85% based on a study identified by Merck Serono.

4.2.16 The Assessment Group's model used utility values derived from the study described in section 4.1.29. The Assessment Group assumed that children in the treated and untreated groups would have no difference in terms of age, sex, social class, weight and long-standing illness, and would differ only in height. Therefore the

Assessment Group derived the utility estimates for health-related quality of life for the treated and untreated groups from the differences in height alone. When estimating cost effectiveness, the Assessment Group used utility values from regression analyses, whereby a gain of 1 height SDS was associated with a change in health-related quality of life utility of 0.061 for people shorter than −2.0 height SDS. For the subgroup with a height SDS between −2.0 and 0.0, an increase in height SDS of 1 was associated with an increase in utility of 0.01.

4.2.17 For people with Prader–Willi syndrome, the Assessment Group considered that treatment with somatropin may be associated with an additional health benefit linked to a change in body composition, which in turn may lead to a reduced likelihood of diabetes and cardiovascular disease. Because of the high uncertainty around the estimates of health-related quality of life, the Assessment Group assumed no benefit associated with a change in body composition in the base case. The Assessment Group also conducted a scenario analysis using changes in utility from a study that found that a one-unit decrease in BMI over 1 year was associated with a gain in utility of 0.017. This value was applied independent of age and sex.

4.2.18 The Assessment Group used costs in the model based upon those used in the model for NICE technology appraisal guidance 42. The Assessment Group assumed an average drug cost of £21.06 in the base case and varied the price in sensitivity analyses from £18.00 to £23.18. Drug costs were calculated according to the dosage recommended and the weight of the child. The Assessment Group obtained weight of children at different ages from the KIGS database.

4.2.19 The ICERs (cost per cm) for the base case were £2798 per cm gained for growth hormone deficiency; £3407 per cm gained for

growth hormone deficiency with treatment continued through the transition phase of early adulthood; £6536 per cm gained for Turner syndrome; £5869 per cm gained for Prader–Willi syndrome; £3696 per cm gained for CRI; £9697 per cm gained for small for gestation age and £8062 per cm gained for *SHOX* deficiency.

4.2.20 The ICERs (cost per QALY gained) for the base case were £23,196 per QALY gained for growth hormone deficiency; £28,244 per QALY gained for growth hormone deficiency with treatment continued through the transition phase of early adulthood; £39,460 per QALY gained for Turner syndrome; £135,311 per QALY gained for Prader–Willi syndrome; £39,273 per QALY gained for CRI; £33,079 per QALY gained for small for gestation age and £40,531 per QALY gained for *SHOX* deficiency.

4.2.21 Sensitivity analyses revealed that, in general, the ICERs were not sensitive to the source of the estimate for clinical effectiveness (that is, whether the data came from the KIGS database or from RCTs). However, using the KIGS database to estimate clinical effectiveness reduced the ICER for somatropin in children born small for gestational age from £33,079 to £18,980 per QALY gained. The Assessment Group noted that the gain in height in children born small for gestational age was higher in the KIGS database than in the RCT.

4.2.22 The discount rates used for the analyses had a large effect on the results. Using discount rates that were used in the model for NICE technology appraisal guidance 42 (that is costs 6% and benefits 1.5%), the costs per QALY gained were less than £30,000 for all the conditions except Prader–Willi syndrome. In addition, for all conditions, the results of the model were most sensitive to age at the start of treatment, length of treatment, adherence and utility gain.

4.2.23 When the lowest available price of somatropin was used in the modelling, the ICERs for growth hormone deficiency, Turner syndrome, Prader–Willi syndrome, CRI, being born small for gestational age and *SHOX* deficiency were reduced to £19,895, £33,766, £115,755, £33,585, £28,296 and £34,664 per QALY gained respectively.

4.2.24 The Assessment Group also presented a scenario analysis for Prader–Willi syndrome that included a life-long change in body composition (BMI) of 1.8 kg/m^2 and an associated additional utility of 0.031. Under this analysis, the cost-effectiveness estimate for Prader–Willi syndrome was £54,800 per QALY gained.

4.2.25 A probabilistic sensitivity analysis undertaken for each of the conditions showed that the mean probabilistic ICERs were slightly lower than the deterministic ICERs for growth hormone deficiency, Turner syndrome, CRI, born small for gestational age and *SHOX* deficiency. The ICER from the probabilistic sensitivity analysis for Prader–Willi syndrome, however, was lower than the deterministic estimate. This was because of non-linearity in the model for Prader–Willi syndrome as a result of the baseline height SDS for the treated group being –2.0, the point at which the utility gain changes. The sampling drew across two different utility gains for height SDS and therefore decreased the ICER in the probabilistic sensitivity analysis.

4.2.26 Probabilistic sensitivity analysis estimated that the probability of cost effectiveness at thresholds of £20,000, £30,000 and £50,000 per QALY gained was 22%, 95% and 100% for growth hormone deficiency, 2%, 19% and 78% for Turner syndrome, 0%, 1% and 8% for Prader–Willi syndrome, 2%, 16% and 80% for CRI, 4%, 38% and 90% for born small for gestational age, and 1%, 15% and 74% for *SHOX* deficiency, respectively.

Summary of cost effectiveness

4.2.27 In the manufacturers' base case the ICERs for somatropin compared with no treatment were below £30,000 per QALY gained for all conditions apart from Prader–Willi syndrome for which the ICER was £32,540 per QALY gained. Using the average price for somatropin in the Assessment Group's model resulted in ICERs of £23,196 per QALY gained for growth hormone deficiency, £39,460 for Turner syndrome, £135,311 for Prader–Willi syndrome, £39,273 for CRI, £33,079 for small for gestational age and £40,531 for *SHOX* deficiency. The additional analysis undertaken by the Assessment Group for Prader–Willi syndrome, which assumed a lifelong change in BMI of 1.8 kg/m^2 and an associated additional utility of 0.031, resulted in an ICER of £54,800 per QALY gained.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of somatropin, having considered evidence on the nature of growth failure associated with growth hormone deficiency, Turner syndrome, Prader–Willi syndrome, CRI, being born small for gestational age and *SHOX* deficiency, and the value placed on the benefits of somatropin by people with growth failure, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.3.2 The Committee examined the evidence of clinical effectiveness presented by the manufacturers and the Assessment Group. It noted that treatment with somatropin resulted in a statistically significant increase in growth in children with the conditions under consideration and a change in body composition in children with Prader–Willi syndrome. The Committee was aware of the limitations of the evidence presented, in that the studies were small, of short duration, and reported no data on health-related quality of life. In addition, the Committee was aware that the

Assessment Group had identified only one study each for growth hormone deficiency and *SHOX* deficiency. However, the Committee concluded that there was sufficient evidence to demonstrate the efficacy of somatropin in promoting growth in children with these conditions.

4.3.3 The Committee heard from the clinical specialists and patient experts that growth failure in children can be associated with considerable stigma, low-self esteem, and learning and behavioural problems during childhood, and in some conditions may also increase the risk of diabetes, cardiovascular disease and osteoporosis later in life. The clinical specialists and patient experts highlighted that, in addition to increasing height and changing body composition, somatropin treatment has a number of other important beneficial effects. These include changes in lipid profile, increase in bone mineral density, behavioural changes, and improvement in self-perception. The Committee therefore concluded that somatropin treatment can, in addition to promoting growth, improve quality of life and may also reduce long-term risk of cardiovascular disease, diabetes and fracture.

4.3.4 The Committee noted that one of the drugs appraised was a 'biosimilar' product (Omnitrope), that is, a new biopharmaceutical product that is similar to an off-patent originator (or reference) biopharmaceutical product (Genotropin). The Committee understood that unlike conventional pharmaceuticals, which can be easily copied by chemical synthesis, biopharmaceuticals are highly complex molecules and are therefore difficult to replicate. The Committee was also aware that because the manufacturer of a 'biosimilar' product does not have access to the exact fermentation and purification process used by the manufacturer of the originator biopharmaceutical product, the originator biopharmaceutical product cannot be copied exactly. The Committee heard that this

may lead to different immunological effects and therefore 'biosimilar' products may have a different safety profile from the originator biopharmaceutical product. The Committee noted that 'biosimilar' products are regulated by the European Medicines Agency (EMEA) via a centralised procedure, whereas generic versions of conventional pharmaceuticals are regulated at national level. The Committee heard that the biopharmaceutical reference product will have been authorised and marketed for several years before the introduction of a 'biosimilar' product. Therefore a substantial amount of information is available for regulatory requirements and this information will not need to be reproduced by the manufacturer of the 'biosimilar' product. It also heard, however, that significantly more data are required for 'biosimilars' than for chemical generic products and that EMEA legislation on 'biosimilars' defines the studies needed to demonstrate equivalent safety and efficacy to the biopharmaceutical reference product. The Committee was aware that making specific recommendations around the safety of a drug was outside the remit of NICE, that no evidence had been submitted on differences between the 'biosimilar' and the originator biopharmaceutical product in terms of safety or efficacy, and that current prescribing advice refers to prescription of biopharmaceutical products by brand name. Based on the marketing authorisation for Omnitrope, the Committee was satisfied that it could consider Omnitrope for the treatment of growth failure alongside the other six somatropin products.

4.3.5 The Committee considered whether there were any differences in the clinical effectiveness of the various somatropin products. The Committee noted that the manufacturer of the 'biosimilar' product (Omnitrope) had undertaken head-to-head trials with the originator product as part of its regulatory submission to the EMEA and that the studies had provided evidence on the equivalence of the two products. The Committee heard from the clinical specialists that

they were not aware of any differences in the products available in terms of safety and efficacy. It also heard that patient choice is an important factor in maximising adherence to therapy. However, the clinical specialists and patient experts highlighted that there appear to be no specific features that determine which product a patient will choose, and that the choice of product depends in part on the choice of delivery system and the support package offered by the manufacturer. The Committee agreed that there appeared to be no differences in the clinical effectiveness of the various somatropin products available. However, it concluded that it would be important to choose the product on an individual basis after informed discussion between the responsible clinician and the patient and/or their carer about the advantages and disadvantages of each product, particularly considering the likelihood of adherence to treatment.

4.3.6 The Committee examined the economic modelling developed for the appraisal by the Assessment Group and by the manufacturers. The Committee was aware that the economic analysis undertaken for NICE technology appraisal guidance 42 did not take into account quality of life and presented cost-effectiveness estimates only in terms of cost per centimetre gained. The Committee understood that TA 42 employed discount rates that are no longer recommended for use in the reference case. The Committee noted that the costs per centimetre gained calculated with the current manufacturers' and Assessment Group's models were more favourable than those reported in the economic evaluation for TA 42.

4.3.7 The Committee discussed the utility values used in the manufacturers' and Assessment Group's economic models and noted that for all conditions except Prader–Willi syndrome these were derived from a single study that estimated utility values

according to height in the general adult population using the EQ−5D. The Committee was disappointed that no attempt appeared to have been made by the manufacturers to measure the quality of life of children with growth failure despite the existence of the KIGS database, and it considered that there were a number of limitations associated with using the utility values from the only study identified. Firstly, the Committee was concerned that the utility estimates reflected the benefits of increased height in adulthood and may not capture the potential increased utility from normal height gain during childhood. Secondly, the Committee was mindful of the testimony from the clinical specialists and patient experts that somatropin treatment provides other benefits in addition to improved height (see section 4.3.3). These additional benefits would not be reflected in the utility values used. Thirdly, the Committee understood that the utility values used in the manufacturers' model were derived from an analysis that did not adjust for possible confounding factors, whereas the Assessment Group used an adjusted analysis from the same study. The Committee was concerned that the utility values from the fully adjusted regression model used by the Assessment Group may have over-corrected with specific reference to chronic illness and social class. Finally, the Committee was not convinced that the impact of short stature would be captured adequately by the areas covered by the EQ–5D (that is, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The Committee agreed therefore that the utility values used in the manufacturers' and Assessment Group's economic models were likely to underestimate both the true disutility associated with growth failure and the utility gain from somatropin treatment.

4.3.8 For Prader–Willi syndrome, the Committee discussed the utility values used in the economic models presented by the manufacturers and the Assessment Group. The Committee noted

that the manufacturers and the Assessment Group (in an exploratory scenario analysis) had modelled additional benefits associated with changes in body composition as well as those from increased height. The Committee agreed that it was appropriate to model the benefits associated with increased height and those associated with changes in body composition because both are included in the licensed indication for Prader–Willi syndrome. The Committee was aware that the manufacturers' economic model allowed an additional utility gain for the reduced diabetes risk associated with changes in body composition. However, the Committee was mindful of the limitations of the study used by the manufacturers to derive the additional utility gain for the reduction in diabetes risk. In the base case the Assessment Group did not include a utility gain associated with a change in body composition in Prader–Willi syndrome. The Committee was aware that children with Prader–Willi syndrome are in general taller at the start of treatment than children with the other conditions considered in this appraisal. The Committee understood that in the Assessment Group's model, utility gains were always lower at the taller end of the height continuum, and that this meant that the utility gains were smaller for Prader–Willi syndrome than those modelled in the base case for the other conditions (see section 4.2.16). The Committee acknowledged that BMI, as used in the Assessment Group's exploratory scenario analysis, is an accepted surrogate marker for obesity because of its broad applicability in the clinical setting; however, the Committee was not persuaded that it adequately captures the benefits associated with changes in body composition with somatropin treatment. The Committee therefore agreed that there were additional uncertainties surrounding the utility value associated with changes in body composition for children with Prader–Willi syndrome, but, as for the other conditions considered

in this appraisal, the utility gains from somatropin treatment were underestimated in the economic models.

4.3.9 The Committee considered the ICERs presented by the manufacturers and the Assessment Group. The Committee noted the large differences between the estimates presented. It recognised that the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources. The Assessment Group used data from RCTs (with the exception of growth hormone deficiency) and the manufacturers used data from the KIGS database. However, the Committee concluded that for most conditions the source of the clinical effectiveness data did not affect the magnitude of the Assessment Group's estimates.

4.3.10 The Committee considered the cost-effectiveness estimates presented by the manufacturers and the Assessment Group for growth hormone deficiency, CRI, Turner syndrome, born small for gestational age and *SHOX* deficiency. The Committee understood that the differences between the cost-effectiveness estimates were driven largely by the different utility values used. However, the Committee agreed that neither the manufacturers' nor the Assessment Group's models took into account the likely true utility gain from increased height in childhood and from additional benefits associated with somatropin treatment (see section 4.3.8), that is, the ICERs presented were likely to be overestimates of the true values.

4.3.11 The Committee then considered separately the ICERs for somatropin for children with Prader–Willi syndrome presented by the Assessment Group and the manufacturers. The Committee noted that the ICER presented in the Assessment Group's base case was substantially greater than that presented by the manufacturers (£135,000 per QALY gained and £32,500 per QALY

gained respectively); this was a much bigger difference than observed for the other conditions. The Committee was aware, however, that the Assessments Group's base-case analysis did not take account of any additional benefits associated with changes in body composition. It noted that when the Assessment Group modelled additional benefits associated with changes in body composition, the ICER for Prader–Willi syndrome was reduced to £54,800 per QALY gained. The Assessment Group presented to the Committee results from deterministic and probabilistic sensitivity analyses of cost effectiveness which differed markedly. The Assessment Group claimed that these differences were a result of non-linearity in the model relating height to EQ–5D for Prader–Willi syndrome. The Committee concluded that although the manufacturers' base case and the Assessment Group's exploratory scenario analysis did take account of some of the additional benefits associated with somatropin treatment, both models underestimated the utility gain (see section 4.3.8). The Committee considered that the true ICER for Prader–Willi syndrome was likely to be considerably less than that derived from the Assessment Group's exploratory analysis.

4.3.12 The Committee was also aware that the ICERs presented by the manufacturers and the Assessment Group were sensitive to variation in the price of the somatropin products. It noted from sensitivity analyses undertaken by the Assessment Group that if the lowest available cost of somatropin was used the ICERs could be further substantially reduced by between £3300 and £19,600 per QALY gained.

4.3.13 Taking the issues around utility values and the variation in price of somatropin into consideration, the Committee agreed that the ICER for somatropin for growth hormone deficiency was likely to fall below £20,000 per QALY, and the ICERs for somatropin for CRI,

Turner syndrome, born small for gestational age and *SHOX* deficiency were likely to be between £20,000 and £30,000 per QALY gained. The Committee acknowledged the uncertainty surrounding the ICER for somatropin for Prader–Willi syndrome, with values ranging from £32,500 (the manufacturers' base-case estimate) to £54,800 (the Assessment Group's exploratory scenario analysis including BMI effects). However, the Committee did not consider that a change in the recommendation made in NICE technology appraisal guidance 42 for the use of somatropin in this disabled and socially marginalised group of children was justified, particularly in light of duties under disability discrimination legislation to have due regard to the need to promote equality of opportunity for disabled people, and to take account of their disabilities. The Committee therefore concluded that within its marketing authorisation somatropin represents a cost-effective treatment for children with growth failure associated with all the conditions under consideration. The Committee also concluded that in light of the apparent equivalence of the clinical effectiveness of the different somatropin products, the least costly product that meets the needs of the individual child and maximises the likelihood of adherence to treatment should be chosen.

4.3.14 The Committee considered the criteria for discontinuing treatment with somatropin. The Committee heard from the clinical specialists that the criteria used for the discontinuation of somatropin in UK clinical practice are consistent with those recommended in NICE technology appraisal guidance 42. It noted that neither the manufacturers' nor the Assessment Group's economic models sought to define rules for discontinuing somatropin treatment, including after attainment of final height as recommended in TA 42. The Committee concluded that criteria for the discontinuation of somatropin treatment should remain in line with those in TA42. Treatment should be discontinued if any of the following apply:

- growth velocity increases less than 50% from baseline in the first year of treatment
- final height is approached and growth velocity is less than 2 cm total growth in 1 year
- there are insurmountable problems with adherence
- final height is attained.

In Prader–Willi syndrome evaluation of response to therapy should also consider body composition.

Treatment should not be discontinued by default. The decision to stop treatment should be made in consultation with the patient and/or carers either by:

  - a paediatrician with specialist expertise in managing growth hormone disorders in children, or
  - an adult endocrinologist, if care of the patient has been transferred from paediatric to adult services.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website

(www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The following trials are currently ongoing:

- Study NCT00190658 aims to compare the mean first year growth velocity of prepubertal children with *SHOX* deficiency treated with somatropin with the growth velocity of a control group of untreated prepubertal children with *SHOX* deficiency. Estimated end date: December 2010.
- Study NCT00625872 focuses on the effect of a 1-year somatropin treatment (35 microgram/kg per day or 67 microgram/kg per day) in short children born small for gestational age on neuromuscular function and cognitive performance. End date not reported.
- There is a controlled cohort study examining health-related quality of life in family members of children prescribed growth hormone treatment for idiopathic growth hormone deficiency, acquired growth hormone deficiency and Turner syndrome. In September 2009, one of the investigators informed NICE that results were not expected until the end of 2010.

6.2 A standardised quality-of-life assessment measuring quality of life in children and in adults is needed for use in future RCTs and studies designed to measure quality of life.

6.3 Good quality research is needed on the long-term effects of somatropin treatment during childhood on body composition, psychological health, diabetes, cardiovascular disease and bone health, and life expectancy, particularly for people with Prader–Willi syndrome.

6.4 Good quality research is needed on somatropin treatment in short children born small for gestational age using dosages of somatropin matching the licensing criteria.

7 Related NICE guidance

Published

- Guidance on the use of human growth hormone (somatropin) in children with growth failure. NICE technology appraisal guidance 42 (2002). Available from www.nice.org.uk/guidance/TA42. This guidance is replaced by (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

8 Review of guidance

8.1 The guidance on this technology will be considered for review by the Guidance Executive in May 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler

Chair, Appraisal Committee

March 2010

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. There are four Appraisal Committees, each with a chair and vice chair. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital, Cambridge

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns
Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Ms Sally Gooch
Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey
Lay member

Mr Sanjay Gupta
YPD Service Case Manager, Southwark Health and Social Care, Southwark Primary Care Trust

Dr Neil Iosson
General Practitioner

Mr Terence Lewis
Lay member

Dr Ruairidh Milne
Director of Strategy and Development, and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Mr Stephen Palmer
Senior Research Fellow, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital and St George's University of London

Mr Philip Pugh
Strategic Development Lead for Healthcare Associated Infection and Antimicrobial Resistance, Health Protection Agency, London

Dr Florian Alexander Ruths
Consultant Psychiatrist and Cognitive Therapist, Maudsley Hospital, London

Mr Navin Sewak
Primary Care Pharmacist, NHS Trust – Hammersmith and Fulham

Dr Lindsay Smith
General Practitioner, East Somerset Research Consortium

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor
Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Ms Nathalie Verin

Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts

Consultant Neurosurgeon, Addenbrookes Hospital, Cambridge

Mr Tom Wilson

Director of Contracting and Performance, NHS Tameside and Glossop

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Fay McCracken and Panagiota Vrouchou
Technical Leads

Nicola Hay
Technical Adviser

Jeremy Powell
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the Southampton Health Technology Assessments Centre:

- 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, August 2009

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Eli Lilly
- Ferring Pharmaceuticals
- Ipsen
- MerckSerono
- Novo Nordisk
- Pfizer Ltd
- Sandoz Ltd

II Professional/specialist and patient/carer groups:

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

III Other consultees:

- Department of Health
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on human growth hormone for the treatment of growth failure in children by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Gary Butler, Professor of Paediatrics and Growth, nominated by the British Society for Paediatric Endocrinology and Diabetes – clinical specialist
- Professor Peter Hindmarsh, Professor of Paediatric Endocrinology, University College London, nominated by the Royal College of Physicians – clinical specialist
- Professor Christopher Kelnar, Professor of Paediatric Endocrinology, University of Edinburgh, nominated by NHS Quality Improvement Scotland – clinical specialist
- Mr Tam Fry, nominated by the Child Growth Foundation – patient expert
- Mrs Arlene Smyth, nominated by the Turner Syndrome Support Society – patient expert