NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Human growth hormone (somatropin) in adults with growth hormone deficiency

1   Guidance

1.1   Recombinant human growth hormone (somatropin) treatment is recommended for the treatment of adults with growth hormone (GH) deficiency only if they fulfil all three of the following criteria.

- They have severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test.
- They have a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire.
- They are already receiving treatment for any other pituitary hormone deficiencies as required.

1.2   The QoL status of people who are given GH treatment should be re-assessed 9 months after the initiation of therapy (an initial 3-month period of GH dose titration, followed by a 6-month therapeutic trial period). GH treatment should be discontinued for those people who demonstrate a QoL improvement of less than 7 points in QoL-AGHDA score.

1.3   Patients receiving GH treatment at the date of publication of this guidance should be re-assessed, as part of routine follow-up, by their consultant endocrinologist, and consideration given to the appropriateness of continuing therapy, taking into account the recommendations in Section 1.1.

1.4 Children with GH deficiency should be treated as outlined in the Institute's guidance on the use of GH in children (*NICE Technology Appraisal Guidance No. 42*). At completion of linear growth (that is, growth rate < 2 cm/year), GH treatment should be stopped for 2–3 months, and then GH status should be re-assessed. GH treatment at adult doses should be re-started only in those satisfying the biochemical criteria for severe GH deficiency (as defined in Section 1.1), and continued until adult peak bone mass has been achieved (normally around 25 years of age). Following this, the decision to continue GH treatment should be based on all the criteria set out in Section 1.1.

1.5 Patients who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years, should be given GH treatment until adult peak bone mass has been achieved, provided they satisfy the biochemical criteria for severe GH deficiency. Following this, the decision to continue GH treatment should be based on all the criteria in Section 1.1.

1.6 Initiation of GH treatment, dose titration and assessment of response during the trial period should be undertaken by a consultant endocrinologist with a special interest in the management of GH disorders. Thereafter, if maintenance treatment is to be prescribed in primary care, it is recommended that this should be under an agreed shared-care protocol.

2 Clinical need and practice

2.1 Growth hormone, also known as somatropin, is a hormone produced by the anterior pituitary gland. It has a role in the regulation of protein, lipid and carbohydrate metabolism, as well as in increasing growth in children. Its secretion is intermittent and occurs predominantly during deep sleep. Secretion reaches maximal levels during adolescence, and then declines with age by approximately 14% per decade.

2.2 Adult GH deficiency may be of adult onset or childhood onset, and may occur as isolated GH deficiency or as part of multiple pituitary hormone deficiency. In adult onset, GH deficiency is commonly due to pituitary tumours or their

treatment, and to cranial irradiation. Childhood-onset GH deficiency is often idiopathic, and may continue into adulthood. Also, iatrogenic GH deficiency may occur in childhood or adulthood in survivors of childhood malignancy, as a result of previous cranial irradiation and/or chemotherapy.

2.3   The Society for Endocrinology estimates that the prevalence of adult-onset GH deficiency is approximately 1 in 10,000 of the adult UK population. If adults with childhood-onset GH deficiency are also considered, the prevalence may be as high as 3 in 10,000 of the adult population. This equates to approximately 12,600 adults with GH deficiency in England and Wales.

2.4   GH deficiency in adults may be associated with the following adverse features to a variable degree in any individual: reduced quality of life (QoL) especially reduced energy levels; altered body composition (reduced lean mass and increased fat mass, especially in the trunk); osteopenia/osteoporosis (reduced bone mineral density); dry skin (reduced sweating); reduced muscle strength and exercise capacity; lipid abnormalities (especially elevated LDL cholesterol); insulin resistance; increased levels of fibrinogen and plasminogen activator inhibitor; reduced extracellular fluid volume; increased thickness of the intima media of blood vessels; and impaired cardiac function.

2.5   Several tests are available for the diagnosis of GH deficiency. The ITT is regarded as the 'gold standard' test for adults. A general definition of severe GH deficiency in adults is a peak concentration of less than 9 mU/litre (3 ng/ml) in response to insulin-induced hypoglycaemia. When the ITT is contraindicated other tests – such as response to GH-releasing hormone, arginine or glucagon – can be used.

2.6   The clinical management of GH deficiency in adults is centred on replacement therapy with biosynthetic human GH (somatropin). However, there has been local variation in practice within the UK. The Society for Endocrinology estimates that approximately 1750 adults with GH deficiency currently receive treatment in the UK.

3 The technology

3.1 There are four preparations of GH available in the UK for the treatment of adults: Genotropin (Pharmacia), Humatrope (Lilly), Norditropin (Novo Nordisk) and Saizen (Serono). Each product is produced by recombinant DNA technology and has a sequence identical to that of human GH.

3.2 GH is licensed for replacement therapy in adults with severe growth hormone deficiency. Patients with severe GH deficiency in adulthood are defined as patients with known hypothalamic pituitary abnormality and at least one known deficiency of another pituitary hormone excluding prolactin. These patients should undergo a single diagnostic test in order to diagnose the presence of GH deficiency. In patients with childhood onset isolated GH deficiency (no evidence of hypothalamic pituitary abnormality or cranial irradiation), two diagnostic tests should be recommended, except for those having low IGF-1 (a marker of GH response) concentrations (standard deviation score less than -2) who may be considered for one test.

3.3 Treatment is self-administered by a daily subcutaneous injection. The initial dose is 0.2–0.3 mg (0.6–0.9 IU) daily (typically 0.27 mg [0.8 IU] daily). For the first 2–3 months dosage adjustments are made after monthly assessments of serum levels of IGF-1, and in response to the presence of adverse effects, until a maintenance dose is achieved. The currently used median maintenance dose is 0.4 mg (1.2 IU) daily. GH requirements may decrease with age.

3.4 Side effects may include headache, arthralgia (joint pain), myalgia (muscle pain), fluid retention (peripheral oedema), mild hypertension, carpal tunnel syndrome, visual problems, nausea and vomiting, paraesthesia, antibody formation, and reactions at the injection site. Benign intracranial hypertension is a rare complication.

3.5 GH treatment is contraindicated in people with any evidence of tumour activity, in critically ill patients (for example, after complications following open

heart or abdominal surgery, multiple trauma, acute respiratory failure or similar conditions) and also in patients with known hypersensitivity to GH or to any of the excipients. GH treatment is also contraindicated during pregnancy and lactation. In patients with tumours, anti-tumour therapy must be completed before starting GH therapy.

3.6 The cost of treatment depends on the dose, which is determined by the weight/size of the patient as well as the individual GH reserve. The cost of GH (excluding VAT; *British National Formulary* [*BNF*] September 2002) is £23.18 per mg for Genotropin, £22.87 per mg for Humatrope and Saizen, and £23.42 per mg for Norditropin. The average annual cost of GH treatment is around £3350 per patient. The cost of treatment reduces with age because the GH requirement decreases as people get older. 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).

The Institute commissioned two Assessment Reports: one was undertaken by the Wessex Institute for Health Research and Development and the other by the University of Sheffield School of Health and Related Research (ScHARR). The Wessex Assessment Report focused on evidence from double-blind, randomised, placebo-controlled trials to evaluate the efficacy of GH treatment in terms of QoL benefits, whereas the ScHARR Assessment Report included the additional evidence that was available from observational studies and some new data from two unpublished randomised controlled trials (RCTs). The Wessex Assessment Report also included a cost analysis of the GH treatment, and the ScHARR Assessment Report provided a detailed critique of the economic models submitted by the manufacturers. During the course of the appraisal some of the manufacturers submitted additional data from newly reported, unpublished trials and results from updated economic analyses.

4.1 Clinical effectiveness

Quality-of-life evidence from randomised controlled trials

4.1.1 The Assessment Reports identified 17 published RCTs evaluating the effects of GH on QoL in around 900 adult patients with GH deficiency. Twenty-three different QoL assessment scales were used, within a variety of trial designs. The duration of the studies was typically 6 months and the number of participants ranged from 6 to 173. Most studies included both adult- and childhood-onset GH deficiency.

4.1.2 Ten studies evaluated health-related QoL using the Nottingham health profile (NHP), but not all reported the results. Additional unpublished data on QoL for one of the studies were made available to ScHARR. These data were supplied in confidence and have not been included in the pooled results presented below. However, including these data had only a small impact on the results of the meta-analyses and did not affect the conclusions of the ScHARR Assessment Report.

4.1.3 The analysis of the individual dimensions of the NHP found some statistically significant changes in the GH-treated group compared with the control group.

4.1.4 In one of the four published studies (the largest) that reported the social isolation dimension, the score was significantly improved in the GH-treated group compared with the placebo group. For this dimension, pooled analysis of all four studies found a small, statistically significant difference in favour of treatment (-0.3 points, 95% confidence interval, -0.4 to -0.1). The largest of the four studies that reported the emotional reactions dimension found a small but statistically significant difference in favour of treatment, but the difference was not statistically significant in the pooled analysis.

4.1.5 Five studies reported the energy dimension. One of the smaller studies found a significant difference in favour of GH treatment, but the pooled analysis of all five did not. For the sleep and physical mobility dimensions, none of the four individual studies reporting these dimensions found a treatment effect of

GH, and nor did the pooled analysis. For the pain dimension, one study found a significant difference in favour of placebo, but there was no significant difference in the pooled analysis of four studies.

4.1.6   The NHP is not designed to produce an overall total score. However, two studies reported mean total scores. Both found improvements in favour of treatment, but these were not statistically significant in either of the individual studies or in the pooled analysis.

4.1.7   Two RCTs used the QoL-assessment of growth hormone deficiency in adults (QoL-AGHDA) questionnaire – a self-completed questionnaire comprising 25 questions specifically designed to assess the consequences of GH deficiency and its treatment. A high QoL-AGHDA score indicates greater impairment of QoL. One study was conducted across three centres in Spain and included 69 patients. The other was conducted in the Netherlands and recruited 30 patients. Minimal data from these studies have been published in abstract form, but further results were made available in confidence to the ScHARR review group for evaluation.

4.1.8   Data pooled from two trials reporting the Hamilton Depression Scale found in favour of GH treatment, but the results were not statistically significant. GH use was associated with an improvement of 2.4 points (95% confidence interval, -4.9 to 0.1).

4.1.9   Meta-analysis of two trials reporting psychological well-being (using the Psychological General Well-being Schedule) found in favour of the GH-treated group, but the results were not statistically significant.

4.1.10 In summary, based on the evidence from RCTs, in terms of QoL the effectiveness of GH treatment in adults with GH deficiency remains unproven. Many of the available studies were of poor quality. Also, because the patients involved had comparatively normal QoL values at baseline there was little scope for improvement. Furthermore, most of the RCTs used a dosage regimen determined by the patient's weight rather than one based on a

titration technique, which is now common clinical practice. This raises difficulties with using this evidence to estimate the effectiveness of currently used GH regimens.

Quality-of-life evidence from observational trials

4.1.11 A 10-year study provided the longest period of observational follow-up of replacement therapy in GH deficiency. This study included patients who had previously participated in an RCT. Of the 24 patients in the original study, ten patients who had received GH continuously for 10 years were compared with 11 who had not. For the group receiving GH, QoL – as measured by the NHP – was improved over baseline in the domains of energy level and emotional reactions. Overall score was also improved. There was no change in the untreated group. However, the two groups may not be comparable because there are several reasons why patients may not continue treatment. Two shorter observational studies (12 months) reported improvements in overall NHP scores after GH treatment.

4.1.12 Eight observational studies of GH therapy in GH deficiency reported QoL-AGHDA scores. Three of these reported results from the largest observational data set of GH-deficient patients, the KIMS database. KIMS is the Pharmacia international metabolic database and pharmaco-epidemiological survey of adult GH-deficient patients receiving GH therapy. The three KIMS studies account for most of the published observational data on QoL. They each included between 300 and 665 participants. However, it is likely that data from many of the same patients were reported in all three publications. The extent to which this may have occurred was not clear. The number of participants lost to follow-up was also unclear. In these studies, the reported mean reduction in QoL-AGHDA score after GH treatment ranged from 2.8 to 4.8. The remaining five studies that used the QoL-AGHDA included between 10 and 65 patients, and reported reductions in mean QoL-AGHDA scores ranging from 3 to 7.2.

4.1.13 A formal meta-analysis of the observational data was not performed. However, a crude estimate of average change in QoL-AGHDA was made. This suggested that, across the studies (weighted by number of patients), the average improvement from baseline in QoL-AGHDA after GH treatment was 3.7 points.

4.1.14 In addition, limited data on specific subgroups (defined according to age and baseline QoL-AGHDA scores) were available from KIMS database. These data suggested that the mean improvement from baseline score in patients less than 65 years of age and with a baseline QoL-AGHDA score of 0-5 was 1.80 points at 1 year. The corresponding values for the groups with baseline QoL-AGHDA scores of 6-10, 11-15, and 15 and over were 5.55, 7.75, and 11.98 respectively, for people less than 65 years old.

4.1.15 In clinical studies, improvements in QoL were observed within 3–6 months of initiating treatment. Limited data from observational studies suggested that the improvement was sustained in the long term (9–10 years) in patients who continued therapy.

4.2 Cost effectiveness

4.2.1 One economic evaluation and three cost studies were identified. The only economic evaluation was reported in an outdated Wessex Development and Evaluation Committee (DEC) report (No. 47, 1995), which had subsequently been replaced by another Wessex DEC report (No. 75, 1997). The latter did not present an economic analysis. The utility element of the economic evaluation presented in the earlier DEC report was a set of scenarios not based on primary or secondary data sources and so could not be considered reliable or valid.

4.2.2 The three cost studies identified were UK-based. One reported costs of diagnosis, GH treatment, and monitoring. The others reported drug costs. All studies reported the cost of the drug as the main factor determining treatment cost (around 90% of total cost). One study reported that annual treatment

costs per patient could vary between £3472 and £6943 (1997 prices and GH dose from 0.125 to 0.25 IU/kg/week), and that costs were sensitive to assumptions about continuation rate and the price of GH. The other two studies reported annual drug costs of GH treatment in the range £3300 to £3453, using more up-to-date (median) drug doses.

4.2.3 A cost analysis was presented in the Wessex Assessment Report and aimed to analyse the average annual and total lifetime costs of GH treatment for a patient starting treatment. There was no attempt to estimate the cost effectiveness (or the cost–utility) of GH treatment. The Assessment Group considered that it was not possible to estimate utility gain – which would ideally be expressed in terms of quality-adjusted life years (QALYs) – with the evidence available from RCTs, and so the analysis was limited to costs. It was estimated that GH treatment in GH-deficient adults costs £3424 annually at an average maintenance dose. The costs of life-long therapy are estimated to be between £42,000 (adult-onset GH deficiency) and £45,400 (childhood-onset GH deficiency) without the cost-savings from hospitalisations prevented, and between £40,500 (adult-onset GH deficiency) and £43,800 (childhood-onset GH deficiency) with the savings from hospitalisations prevented. These estimates assume that 20% of people discontinue GH treatment after 6 months.

4.2.4 Drug therapy was found to be the single most important factor in determining cost; changes in the price of GH significantly altered treatment costs, so any price reductions could result in cost savings for the NHS. It was noted that the price at local level could significantly differ from the *BNF* list price, but there were no reliable data to inform the analysis.

4.2.5 Three manufacturers submitted economic evaluations to the Institute; all three estimated the cost–utility of GH use in adults (that is, they expressed the benefits of treatment in terms of QALYs). One also expressed cost effectiveness in the form of cost per normalised life-year gained.

4.2.6   Two economic models (Lilly and Novo Nordisk) adopted the methods used in the Wessex DEC report to generate utility estimates. The cost–utility ratios estimated by these models were between £4500 and £32,000 per additional QALY gained. These models did not use primary data but were based on estimates of the likely utility gains, for which there is little evidence. The models should therefore be treated with caution.

4.2.7   One manufacturer's model estimated the cost effectiveness to be £15,648 per additional normalised life-year for adult-onset GH deficiency, and £16,522 per additional normalised life-year for childhood-onset GH deficiency. The data came from pre- and post-treatment scores of 124 UK patients using the questions on life satisfaction modules for hypopituitarism questionnaire (QLS-H) – a new QoL instrument for adults with GH deficiency, which covers nine domains. 'Normalisation' of QoL was defined as achieving a 'somewhat satisfied', 'satisfied' or 'very satisfied' score in all domains.

4.2.8   Another manufacturer's model estimated the cost effectiveness of the use of GH replacement therapy in adults to be between £27,500 and £37,600 per additional QALY gained. This model used some inputs (especially those related to cardiovascular and fracture risks) derived from a simulation model, which was also provided. Utility estimates were derived from QoL data collected in the KIMS database. Because the QoL-AGHDA questionnaire is not designed to produce preference-based utilities, regression analysis was used to convert the available data into utility scores. Sub-group analyses for different age and QoL groups were also presented. It should be noted that the use of regression analysis to derive the utility scores is limited by the quality of the data from which they are estimated and the degree of overlap of the descriptive systems.

4.2.9   The economic analysis presented by ScHARR demonstrated that the long-term effects on risk factors for fractures and cardiovascular events had very little impact on the cost effectiveness of GH treatment. The ScHARR report also included a series of sensitivity analyses to investigate the impact on the

results of relaxing the manufacturers' assumptions, which were regarded as optimistic.

4.2.10 The ScHARR estimate of the impact of GH treatment on QoL was based on the use of observational data using the QoL-AGHDA questionnaire. This was regarded as an optimistic scenario because observational data are very prone to overestimate the treatment effect, particularly for subjective outcomes for which the placebo effect may be especially problematic. A similar mapping exercise to that used in one of the manufacturer's analyses (see Section 4.2.8) was used to derive the utility scores. Additional QoL data made available to ScHARR by one of the manufacturers measured the benefits by using the QLS-H questionnaire, but there is currently no method to map these findings to utility scores.

4.2.11 The ScHARR analysis, based on an overall utility gain of 0.04–0.12 depending on age and baseline QoL score, estimated the cost effectiveness of GH therapy to be between £25,300 (for people aged 65 years or older with a QoL-AGHDA score ≥ 16) and £124,950 (for people aged 18–30 years with a QoL-AGHDA score of 6–10). The overall cost effectiveness of GH therapy was estimated to be in the region of £45,000 per additional QALY. This figure is very sensitive to the estimate of effectiveness, and it should be regarded as the best-case scenario because it is based on observational data that are likely to overestimate the benefits of treatment.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of GH treatment in adults with GH deficiency, having considered evidence on the nature of the condition and the value placed on the benefits of GH treatment from adults with GH deficiency, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.

4.3.2 The Committee considered in detail the significance of the effectiveness of GH treatment in GH-deficient adults in terms of its effects on QoL. In addition, the Committee considered the potential effect of GH deficiency on clinical parameters that might adversely affect cardiovascular risk profiles or the potential for bone fractures caused by reduced bone mineral density, both of which might adversely affect life expectancy. The possibility that GH deficiency might also contribute to a higher overall standardised mortality ratio (SMR), over and above that which can be attributed to the effects on cardiovascular risk and bone mineral density, was also taken into account.

Effects of GH replacement on quality of life

4.3.3 The Committee considered that improvement in QoL was an important, if not the only, determinant of the clinical and cost effectiveness of GH treatment. It therefore considered at length the assessment tools for QoL used in studies of GH therapy, and in particular the appropriateness and suitability of the NHP, QLS-H, EQ-5D and QoL-AGHDA scoring systems. In addition, the Committee reviewed the evidence on QoL effects from both the RCTs and the observational studies. The Committee was also aware of the high compliance rates among GH users (reported to be around 92%), as pointed out by both the patient representatives and experts.

4.3.4 It was acknowledged that there were inconsistencies between the results of RCTs, observational studies, and the accounts of many individual patients about the effect of GH therapy on QoL. The Committee took into account the deficiencies in the evidence from RCTs. In particular, the Committee considered the possibility that a sub-group of patients – those with very poor QoL – were benefiting from treatment, but that the effect in these patients was obscured by the inclusion of a large proportion of patients with relatively good pre-treatment QoL and hence little scope for improvement.

4.3.5 During the course of this appraisal, the Committee was presented with several analyses relating to improvement in QoL (in addition to the original submissions) that attempted to identify a subgroup of patients in whom GH

therapy would be cost effective (that is, those who would gain an improvement in QoL much larger than the average improvements seen in RCTs and observational studies). The Committee reviewed data from an updated subgroup analysis based on a postal survey using the EQ-5D questionnaire of 197 people with GH deficiency. This re-analysis suggested that improvement in utility due to GH treatment might be up to 40% greater than that estimated by QoL-AGHDA. The Committee also reviewed additional data based on QLS-H assessments (from the Hypopituitary Control and Complication Study database). The results from this analysis also suggested that there was likely to be a subgroup of people with GH deficiency who would gain greater improvements in QoL on GH replacement. However, it was not possible to map the data from QLS-H scores into utilities, so this did not provide further direct information to inform the analysis of the cost effectiveness of this technology for selected subgroups.

4.3.6   The Committee accepted that, although there was not sufficient information available to it to enable a detailed evaluation of the quality of the methods used to derive the new EQ-5D data, a greater degree of utility change using EQ-5D than using QoL-AGHDA would be anticipated because of the well-established differences in the properties of these two QoL tools. The Committee considered that these additional data suggested that a minimum improvement of at least 7 points in QoL-AGHDA score from baseline would be needed to achieve an acceptable level of cost effectiveness.

Effects of GH replacement on mortality

4.3.7   The Committee considered in detail the effect of GH replacement on overall mortality from various causes in people with GH deficiency. It considered the potential deleterious effects of GH deficiency on cardiovascular risk profiles and bone mineral density, as well as data on SMRs for people with GH deficiency compared with matched populations. The Committee noted that the association between increased mortality and GH deficiency was based on

uncontrolled, observational data and on the assessment of cohorts from different periods.

4.3.8 The Committee concluded that it was uncertain what impact GH treatment had on the longer-term clinical outcomes and mortality related to cardiovascular risk factors and changes in bone mineral density. However, the Committee believed that the best available evidence from observational studies of these risk factors on mortality had been included in the overall estimates of cost effectiveness that it had reviewed. The Committee considered that it was problematic to draw conclusions about the impact of isolated GH deficiency on overall SMRs (that is, mortality over and above that attributable to cardiovascular risk and bone mineral density changes), because the populations reported in different studies were heterogeneous, which made comparisons difficult. In addition, the SMR data were not adjusted for potential confounding factors, and causality could not be clearly explained.

Summary of considerations for adult-onset GH deficiency

4.3.9 The Committee was persuaded that there was a subgroup of people with GH deficiency whose QoL was significantly impaired, and for whom the benefits of GH replacement could be both clinically and cost effective. However, the effect of treatment on overall mortality was less certain and, on the basis of the present evidence, was likely to have been accounted for predominantly by taking into account effects on cardiovascular risk profiles. While accepting that other factors directly or indirectly affecting overall mortality may be present in GH-deficient people, the Committee believed that these would need to be explored in future research.

4.3.10 The Committee reviewed the analyses of cost effectiveness of GH replacement in adult-onset GH deficiency, including the updated analysis submitted by one manufacturer, that assessed in detail the various factors that might influence the calculations of incremental cost-effectiveness ratios (ICERs), including QoL utility estimates based on different methodologies, the

potential effects on overall mortality and the appropriateness of modelling benefits over different time periods.

4.3.11 After reviewing the updated cost-effectiveness analyses, and the data from the KIMS database on the levels of improvement (in terms of QoL-AGHDA scores) for different patient groups, the Committee considered that the subgroup of people with GH deficiency for whom treatment may be cost effective would be those who had an improvement in QoL equivalent to an absolute change in their baseline QoL-AGHDA score of at least 7 points. The Committee considered that the ICER for this group of patients would be in the region of £25,000 to £45,000 per QALY.

4.3.12 The Committee agreed, on the basis of testimony from the experts, that the QoL-AGHDA questionnaire was the best available evaluation tool for the assessment of both baseline QoL and the effect of treatment in people with GH deficiency. The Institute sought clarification on the availability of the QoL-AGHDA questionnaire for use by the clinical community from the developer, Pharmacia, who provided a written statement confirming that the questionnaire is freely accessible as a clinical tool across the UK.

4.3.13 The Committee considered at length the issue of the baseline score of QoL-AGHDA that would identify the subset of people with severe GH deficiency for whom GH treatment would most clinically and cost effective. It took into account a variety of factors, including the information from the KIMS database and specifically the data that showed that an improvement of an average of 7 points in QoL-AGHDA was only documented in patients with a baseline QoL-AGHDA score of 11 or more. This, together with consideration of the effect of GH on QoL (see Sections 4.3.3 to 4.3.6) led the Committee to conclude that a trial of GH treatment could be recommended for people with GH deficiency who have a severe perceived impairment of QoL as demonstrated by a reported score of at least 11 in QoL-AGHDA.

4.3.14 The Committee was persuaded by the evidence from expert endocrinologists that reassessment of the need for GH replacement should take place after a

trial treatment period of 9 months (3 months for dose titration and 6 months for assessment of response). For GH treatment to continue after this trial period, it should be necessary to demonstrate a sustained improvement in QoL.

4.3.15 In considering the minimum requirement for the degree of QoL improvement at the end of the trial period, the Committee took into account the data from the KIMS population, the cost-effectiveness considerations (see Section 4.3.11), and the views from the patient/carer organisations and the clinical experts. The Committee concluded that, on the balance of probabilities, an improvement during the trial with GH of 7 points or more in QoL-AGHDA score compared with the baseline measurement would be needed to justify the clinical and cost effectiveness of continuing GH treatment beyond the trial period.

4.3.16 The Committee was aware that in the KIMS population the QoL improvement score of 7 in patients with a baseline QoL-AGHDA score of 11 or more was a mean value, which implies that there will be some people in this group who did not improve by 7 points and others who improved by more than 7 points. However, the Committee considered – on the basis of all the evidence it had reviewed, the uncertainties surrounding the precise definition of the subgroup that would most benefit from GH treatment, and the extent of any such benefit – that cost-effectiveness should be evident for individual patients. Thus in patients who demonstrate an improvement score lower than 7 points, the Committee concluded that cost effectiveness was not established, and the continued use of GH in these patients after the initial assessment period could not be justified.

Transitional period

4.3.17 The Committee considered the issues related to the treatment arrangements for those with childhood-onset GH deficiency from all causes, and the value of GH treatment after the completion of linear growth. It was agreed that people with childhood-onset GH deficiency should be re-tested after the attainment of

final height to assess whether they are eligible for further GH replacement (see Section 1.1).

4.3.18 The Committee was persuaded by evidence from experts that, for people with childhood-onset GH deficiency who had completed linear growth but still remained severely deficient in GH according to biochemical tests, treatment with GH should be continued until adult bone mass is achieved. The Committee accepted that there are likely to be significant disadvantages in later life for those who do not achieve peak adult bone mass, although this conclusion was not fully evidence-based. The Committee additionally accepted, on the basis of expert testimony, that the age at which peak adult bone mass is achieved can vary between 25 and 30 years depending on a number of factors, including the age of puberty.

4.3.19 The Committee concluded, therefore, that there will be a proportion of people with childhood-onset GH deficiency for whom continuation of treatment until peak adult bone mass is achieved is desirable. Thereafter, GH treatment should be discontinued and only recommended on the basis of the criteria laid down for adult-onset GH deficiency (see Section 1.1).

4.3.20 The Committee was aware of clinical differences between children with idiopathic isolated GH deficiency (IIGHD) and those with multiple pituitary hormone deficiencies, including GH (MPHD). It was, however, not persuaded that there was sufficient evidence that they should be treated differently during the transition period. They concluded, therefore, that during the transition phase all childhood-onset GH deficiency should be managed as indicated in Section 1.4 of this guidance – stopping GH treatment once adult bone mineral density had been achieved and restarting treatment only on the basis of the criteria laid down for adult-onset GH deficiency (see Section 1.1). The possibility that children with IIGHD or MPHD should be treated differently within these criteria could be the subject of further research.

4.3.21 The Committee considered the situation of people who develop GH deficiency in early adulthood after linear growth is completed, but before the age of

25 years. These people may require additional GH treatment in order to achieve full adult levels of bone mineral density. The Committee concluded that people in this period of 'transition' should be treated appropriately with GH, and then the criteria in Section 1.1 should apply for consideration of further GH therapy.

5 Further research

5.1 Further good-quality studies are needed in the following areas.

- To investigate whether titrated-dose GH therapy improves QoL more than placebo in GH-deficient adults, and to quantify the treatment effect more accurately.

- To ascertain the most sensitive way of measuring the QoL gain in GH-treated adults, particularly with regard to generating preference-based utilities.

- To investigate the relationship between SMR and GH deficiency for both adult-onset and childhood-onset GH deficiency, as well as for different subgroups.

- To investigate whether patients with MPHD and idiopathic isolated GH deficiency have different treatment requirements, in order to achieve cost effective use of GH treatment.

- To investigate whether different treatment criteria are warranted for childhood and adult onset GH deficiency, in order to optimise the benefits from GH treatment.

6 Preliminary views on the resource impact for the NHS

6.1 Although it is hard to estimate the number of eligible patients accurately, it is anticipated that only a small proportion of adults with GH deficiency will achieve sustained improvement of at least 7 points on the QoL-AGHDA scale at the end of the assessment period (that is, 9 months). If it is assumed that

30% of adult-onset and 10% of childhood-onset patients will fulfil the starting criteria, and of these 40% will fail to achieve an improvement of at least 7 points on the QoL-AGHDA scale, there will be around 1180 people in England and Wales who would be eligible for continuous GH treatment. This is less than the estimated number of patients currently receiving GH treatment, so implementing this guidance will not incur any additional costs to the NHS. However, in the absence of more accurate data on future uptake, it is not possible to indicate the scale of any potential savings.

7 Implementation and audit

7.1 Clinicians who provide care for adults with GH deficiency should review policies and practices regarding the prescription of GH in adults to take account of the guidance set out in Section 1.

7.2 Local guidelines and care pathways on the treatment of adults with GH deficiency should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria can be used. Further details on suggestions for audit are presented in Appendix C.

7.3.1 Recombinant human growth hormone (somatropin) treatment is given to an adult with GH deficiency only if he or she meets all three of the criteria 7.3.1.1–7.3.1.3 or criterion 7.3.1.4.

    7.3.1.1 The individual has severe GH deficiency, defined as having a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test (ITT) or a cross-validated GH threshold in an equivalent test.

    7.3.1.2 The individual has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific QoL-assessment of growth hormone deficiency in adults (QoL-AGHDA) questionnaire.

7.3.1.3   The individual is already receiving treatment for any other pituitary hormone deficiencies as required.

7.3.1.4   The individual is receiving GH treatment at the date of publication of this guidance and, following re-assessment by his or her consultant endocrinologist as part of routine follow-up, it is considered appropriate to continue the therapy, taking into account the guidance in Section 1.1.

7.3.2   An adult who is started on GH treatment is re-assessed for QoL status 9 months after the initiation of therapy. GH treatment is discontinued if the individual has a QoL improvement of less than 7 points in QoL-AGHDA score.

7.3.3   For an individual who as a child has been treated for GH deficiency and who has completed linear growth, the following are done.

7.3.3.1   GH treatment is stopped for 2–3 months.

7.3.3.2   The GH status of the individual is re-assessed.

7.3.3.3   GH treatment at an adult dose is re-started only if the individual has a peak GH response of less than 9 mU/litre (3 ng/ml) during an ITT, or a cross-validated GH threshold in an equivalent test.

7.3.3.4   If GH treatment is re-started, GH treatment at an adult dose is continued until adult peak bone mass is achieved.

7.3.3.5   When adult peak bone mass is achieved, GH treatment is continued only if the individual meets criteria 7.3.1.1–7.3.1.3.

7.3.4   For an individual who develops GH deficiency in early adulthood, after linear growth is completed but before the age of 25, the following are done.

7.3.4.1   GH treatment should be given until adult peak bone mass is achieved if the individual has a peak GH response of less than

9 mU/litre (3 ng/ml) during an ITT, or a cross-validated GH threshold in an equivalent test.

7.3.4.2   When adult peak bone mass is achieved, GH treatment is continued only if the individual meets criteria 7.3.1.1–7.3.1.3.

7.3.5   The following are carried out only by a consultant endocrinologist with a special interest in the management of GH disorders.

- Initiation of GH treatment.
- Dose titration.
- Assessment of response during the trial period.

7.3.6   If maintenance GH treatment is to be prescribed in primary care, there is an agreed shared-care protocol.

8   Related guidance

8.1   The Institute issued guidance in May 2002 on the use of GH treatment in children with growth failure.

- National Institute for Clinical Excellence (2000) Guidance on the use of human growth hormone (somatropin) in children with growth failure. *NICE Technology Appraisal Guidance* No. 42. London: National Institute for Clinical Excellence. Available from www.nice.org.uk

9   Proposed date for review of guidance

9.1   The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2   It is proposed that the guidance on this technology is reviewed in June 2006.

David Barnett

Chair, Appraisal Committee

April 2003

Appendix A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. 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 twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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 Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor Sir Colin Berry (term of office ended October 2002)
Retired Professor of Morbid Anatomy & Histopathology, The Royal London Hospital

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Professor Rosamund Bryar
Professor of Community & Primary Care Nursing, St Bartholomew's School of Nursing & Midwifery, London

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich

Professor Sarah Cowley (term of office ended October 2002)

Professor of Community Practice Development, Kings College, London

Professor Nicky Cullum (up to January 2002)

Professor in Health Sciences/Director, Centre for Evidence-based Nursing, University of York

Mr Chris Evennett (up to June 2002)

Chief Executive, Mid-Hampshire Primary Care Trust, Winchester

Professor Terry Feest

Clinical Director & Consultant Nephrologist, Richard Bright Renal Unit, & Chair of UK Renal Registry, Bristol

Professor Gary A Ford

Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Ms Jean Gaffin (up to February 2002)

Formerly Executive Director

National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher (term of office ended October 2002)

Former Chief Executive, Merton, Sutton & Wandsworth Health Authority, London

Ms Bethan George

Interface Liaison Pharmacist, Tower Hamlets PCT and Royal London Hospital, Whitechapel

Dr Cathryn Thomas

General Practitioner, & Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

Appendix B. Sources of evidence considered by the Committee

A   The assessment reports for this appraisal were prepared by:

    I   Southampton Health Technology Assessment Centre, University of Southampton

- *Clinical and cost effectiveness of growth hormone in adults: Quality of life*, October 2001

    II   School of Health and Related Research (ScHARR), University of Sheffield

- *Clinical and cost effectiveness of recombinant human growth hormone (somatropin) in adults*, April 2002
- *Response to comments received from consultees responding to the post appeal considerations for the clinical and cost effectiveness of recombinant human growth hormone (somatropin) in adults*, January 2003

B   The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report. They are also invited to comment on the ACD and consultee organisations are provided with the opportunity to appeal against the FAD.

    I   Manufacturer/sponsors:

- Eli Lilly
- Novo Nordisk
- Pharmacia

    II   Professional/specialist and patient/carer groups:

- British Society for Paediatric Endocrinology and Diabetes

- Department of Diabetes, Endocrinology and General Medicine, The Guy's, King's College and St Thomas' Hospitals Medical and Dental School
- Department of Health & Welsh Assembly Government
- NHS Quality Improvement Scotland
- Pituitary Foundation
- Restricted Growth Association
- Royal College of Paediatrics and Child Health
- Royal College of Physicians
- Society for Endocrinology

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. 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 (somatropin) in adults with growth hormone deficiency by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Gary Butler, Consultant Paediatric and Adolescent Endocrinologist, Leeds General Infirmary
- Dr Charles R Buchanan, Consultant Paediatric Endocrinologist, King's College Hospital, London
- Dr Janet Harbour, Pituitary Foundation
- Ms Patsy Perrin, Vice-Chair, Pituitary Foundation
- Professor D G Johnston, Department of Endocrinology and Metabolic Medicine, Imperial College School of Medicine and St Mary's Hospital
- Professor John Monson, Consultant in Endocrinology, St Bartholomew's Hospital, London
- Professor John Wass, Chair of Clinical Committee, Society for Endocrinology

- Professor M C Sheppard, Professor of Medicine and Head of Division, Queen Elizabeth Hospital, Birmingham
- Professor Paul Stewart, Consultant Endocrinologist, Queens Medical Centre, Birmingham
- Professor Richard Ross, Professor of Endocrinology, Northern General Hospital, Sheffield
- Professor Steven Shalet, Consultant Endocrinologist, Christie Hospital, Manchester
- Sue Thorn, Honorary Secretary, Pituitary Foundation

Appendix C. Detail on criteria for audit of the use of human growth hormone (somatropin) in adults with growth hormone deficiency

Possible objectives for an audit

An audit on the appropriateness and effectiveness of the use of growth hormone (GH) treatment in adults with GH deficiency could be carried out to ensure the following.

- GH treatment is given to an adult with GH deficiency only if he or she meets defined criteria.
- An adult who is started on GH treatment is re-assessed and GH treatment is discontinued if there is an insufficient improvement in quality of life (QoL).
- Continued GH treatment is given only in appropriate circumstances to an individual who has been treated for GH deficiency as a child and who has completed linear growth.
- GH treatment is given to an adult who develops GH deficiency in early adulthood only in appropriate circumstances.
- Initial treatment of adults with GH deficiency is done only by a qualified specialist and maintenance GH treatment is continued in primary care only when there is an agreed shared-care protocol.

Possible patients to be included in the audit

An audit could be carried out on all adults referred or seen for GH deficiency in a given time period, for example, 6 months or a year. Because the measures listed below refer to care provided after the start of GH treatment, it may be desirable to limit the audit to new patients or to agree on the specific time period of care that will apply to each of the measures.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of GH treatment are as follows.

Criterion	Standard	Exception	Definition of terms
1. An adult given recombinant human growth hormone meets **all three** of a–c **or** d as follows: a. The individual has severe GH deficiency *and* b. The individual has a perceived impairment of quality of life (QoL) as demonstrated by a reported score of at least 11 in the QoL-AGHDA questionnaire *and* c. The individual is already receiving treatment for other pituitary hormone deficiencies as required *or* d. The individual is receiving GH treatment at the date of publication of this guidance and, following re-assessment, it is considered appropriate to continue the therapy	100% of the adults who are on recombinant human growth hormone	None	'Recombinant human growth hormone' means somatropin. 'Severe GH deficiency' means having a peak GH response of less than 9 mU/litre (less than 3 ng/ml) during an insulin tolerance test (ITT) or a cross-validated GH threshold in an equivalent test. For b, see the individual's self-reported score on the QoL-AGHDA questionnaire. For d, 're-assessment' means by the individual's consultant endocrinologist as part of routine follow-up. For d, 'appropriate to continue' assumes that the consultant considers the criteria stated in 1a–1c. Clinicians will have to agree locally on how consideration of the appropriateness of continuation of therapy, for patients on GH therapy at the date of publication of this guidance, is documented for audit

				purposes.
2.	An adult who is started on GH treatment:			Clinicians will have to agree locally how far back in time care is to be reviewed for this criterion, and on where QoL status at 9 months after initiation of therapy will be documented for audit purposes (that is, where the QoL–AGHDA questionnaire scores are ordinarily recorded). '9 months after the initiation of therapy' means after an initial 3-month period of GH dose titration followed by a 6-month therapeutic trial period.
a.	Is re-assessed for QoL status 9 months after the initiation of therapy	100% of the adults started on GH treatment within the time period agreed for audit purposes	None	
b.	Has GH treatment discontinued if the individual has a QoL improvement of less than 7 points in QoL-AGHDA score	100% of the adults started on GH treatment within the time period agreed for audit purposes who have insufficient QoL improvement	None	
3.	The following are done for an individual who as a child was treated for GH deficiency and who has completed linear growth:			'Completion of linear growth' means growth rate <2cm/year. 'Re-assessed' means for GH status and QoL as defined in 1 above. Adult peak bone mass is normally achieved by about 25 years of age.
a.	GH treatment is stopped for 2–3 months *and*	For 3 a and b: 100% of the individuals who have been treated for GH deficiency as a child and who have completed linear growth	For 3 a and b: None	
b.	The GH status of the individual is re-assessed *and*			
c.	GH treatment at an adult dose is re-started only if the individual	For 3 c and d: 100% of the individuals	For 3 c and d: None	

meets criterion 1a above ***and*** d. GH treatment at an adult dose is continued until adult peak bone mass is achieved ***and***	who have been treated for GH deficiency as a child, who have completed linear growth and who have GH treatment restarted		
e. When adult peak bone mass is achieved, GH treatment is continued only if the individual meets criteria 1a–c above	For 3 e: 100% of the individuals who achieve adult peak bone mass and who have GH treatment continued	For 3 e: None	
4. The following are done for an individual who develops GH deficiency in early adulthood after linear growth is completed but before the age of 25: a. GH treatment is given until adult peak bone mass is achieved if the individual meets criterion 1a above ***and*** b. When adult peak bone mass is achieved, GH treatment is continued only if the individual meets criteria 1a–1c above	100% of the individuals who develop GH deficiency in early adulthood after linear growth is completed but before the age of 25		See 1 above for definition of GH deficiency and see 3 above for definition of adult bone mass.
5. The following are carried out by a qualified specialist: a. Initiation of GH treatment ***and***	100% of the individuals who are given GH therapy	None	A 'qualified specialist' is a consultant endocrinologist with a special interest in the management of GH disorders.

b. Dose titration **and**			Clinicians will have to agree locally how far back in time care is to be reviewed for this criterion.
c. Assessment of response during the trial period			
6. If an individual's maintenance GH treatment is prescribed in primary care, there is an agreed shared-care protocol	100% of individuals seen for maintenance prescription in primary care	None	Clinicians will have to agree locally on what constitutes agreement on a shared-care protocol.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the } \textbf{criterion } \textit{plus} \text{ number of patients who meet any } \textbf{exception} \text{ listed}}{\text{Number of patients to whom the } \textbf{measure} \text{ applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.