NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Eli Lilly	Thank you for sending us the Appraisal Consultation Document (ACD) on Humatrope (somatropin) for the treatment of growth failure in children and for the opportunity to comment on it.	Comment noted.
	We are pleased with the recommendations made by the Committee as set out in the ACD and look forward to a positive final recommendation from NICE after the second Appraisal Committee meeting.	Comment noted.
	We are also happy that the Committee concluded that there is sufficient evidence to demonstrate the efficacy of somatropin in promoting growth in children. RCTs are generally not appropriate to capture long term outcomes. This is particularly the case in growth failure where longer term outcomes such as final height need extensive follow up. The recommendation from NICE that further research is needed to collect long term evidence should take a more pragmatic approach allowing for observational studies such as the KIGS database to be considered.	Comment noted.

Consultee	Comment	Response
Eli Lilly	The Committee acknowledged a purely 'utility' based approach is likely to underestimate the true impact of treatment on the health and wellbeing of individuals with growth failure. Lilly welcomes this approach as somatropin provides broader health benefits that could improve patient QoL and wellbeing that are difficult to quantify but make all the difference to patients with this condition including self-esteem, improved lean body mass, bone mass and muscle strength to name a few. Section 4.2.5 states the manufacturers model is an extension of model from 2002. The model developed by Pfizer as part of the Collaboration of 5 of the manufacturers was a de novo Markov economic model. This needs correcting.	Comment noted. Comment noted. FAD section 4.2.5 has been amended.
Ferring	Thank you for allowing Ferring to comment on the Appraisal Consultation Document on Growth failure (in children) - human growth hormone (HGH) (review). Ferring have no comments to make on this. We thank NICE for allowing us this opportunity for comment on this document.	Comment noted.
Merck Serono	Merck Serono appreciates the opportunity to comment on the ACD. We feel that it is a thorough consideration of the evidence on clinical and cost effectiveness of Human Growth Hormone (HGH) in this setting and welcome the positive recommendations. We would like to provide minor comments on a few areas: the description of biosimilars; long term studies on the effectiveness of growth hormone; the manufacturer's model; the utilities used in the model; the review date for the guidance.	Comment noted. See below for response to detailed comments.

Consultee	Comment	Response
Merck Serono	**Description of biosimilars** In sections 4.3.5 and 4.36 the Institute gives a description around biosimilars, and states that 'making specific recommendations around the safety of a drug was outside the remit of NICE.' Although Merck Serono agree with this statement, we feel that it may be helpful to record the official description of biosimilars as per the BNF for scientific accuracy. In the BNF no. 58 it states that 'a biosimilar medicine is a new biological product that is similar to a medicine that has already been authorised to be marketed (the biological reference product) in the European Union. The active substance of a biological medicine is similar, but not identical, to the reference medicine. Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no meaningful 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 automatic substitution of a biological medicine does not occur when the medicine is dispensed.'	Comment noted. The 'consideration of the evidence section' has been amended to provide greater clarification on the manufacturing process and regulatory environment of 'biosimilar' products. See FAD section 4.3.4. Comment noted. FAD Section 3.2 has been amended to include the advice given in the British National Formulary regarding the prescribing of biopharmaceutical products by brand-name.
	Long term effectiveness studies Although there is a lack of studies published examining the long-term effectiveness of HGH in these indications as noted in the ACD, there are a few long-term observational databases available. These include KIGS (Kabi International Growth) database, which has been used in the manufacturer model and mentioned by the Institute in the ACD.	Comment noted. The Committee noted that the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources. However, the Committee concluded that the source of the clinical effectiveness data did not affect the magnitude of the Assessment Group's cost effectiveness estimates for the majority of the conditions. See FAD section 4.3.9.

Consultee	Comment	Response
Merck Seono	**The manufacturers' model** There are two points of accuracy we want to bring to the Institute's attention. Firstly under 4.2.5 it states that the model was based upon the one for NICE Technology Appraisal Guidance 42. In fact the model submitted in the review was constructed de novo to incorporate analysis of QALYs gained as requested in the NICE reference case. Secondly Merck Serono did not produce their own version of the model. The only aspect that differed from the core model was the costs were adjusted in the main analysis presented to take into account the potential waste elimination benefit of the EasypodTM delivery device	Comment noted. FAD section 4.2.5 has been amended.
	The utilities and costs in the model Merck Serono appreciate that the Institute has acknowledged the difficulties in finding utilities relevant for the analysis of the cost-effectiveness of HGH, and particularly that our conservative approach could not account for the additional benefits such as those on self-esteem and body composition. Therefore it was appropriate for social value judgements to be applied.	Comment noted.
	The review date for this appraisal Merck Serono feel that a review date of May 2013 will likely be too early for this appraisal. We would suggest that 2014 may be more appropriate.	Comment noted. The review date refers to when we will consider reviewing the guidance. During this period, the institute will identify any new evidence available and trials that are due for completion. The Institute will then determine whether and when a review of this guidance should be undertaken.

Consultee	Comment	Response
Novo Nordisk	Thank you for allowing Novo Nordisk to comment on the Appraisal Consultation Document (ACD) for the above review. We have the following comments regarding the ACD under the appropriate headings. **I. Do you consider that all of the relevant evidence has been taken into account?** Novo Nordisk believes that the committee has fairly concluded that sufficient evidence was available to demonstrate the efficacy of somatropin. Nevertheless, more long-term evidence (including final height data) would have been available for consideration had the Assessment group expanded the inclusion criteria of its systematic review to include dose-ranging studies. This would have been appropriate in this instance as long-term RCTs comparing somatropin with a placebo/untreated group are considered unethical.	Comment noted. See below for response to detailed comments. Comment noted.

Consultee	Comment	Response
Novo Nordisk	**II. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?**	
	Novo Nordisk is pleased that the committee has acknowledged the difficulties associated with the calculation of utility scores to reflect the impact of short stature and the benefits of somatropin other than height gains. We therefore believe that it is appropriate that the committee has concluded that the true cost-effectiveness of somatropin is likely to fall within the range normally considered acceptable.	Comment noted.
	In section 4.2.17, the cost per cm gained for small for gestational age is stated to be £9697. However, as pointed out in our comments on the Assessment report, this calculation is based on 1 year of height gains and 6 years of treatment costs. The cost per cm gained using comparable time horizons for costs and benefits should be presented.	Comment noted. In its response to comments on the Assessment report, the Assessment Group stated that it accepted the consultees' point that it is inconsistent to use the 1 year RCT data in the base case analysis for the children born small for gestational age model and amended the wording in the report to make a clearer justification. The Assessment Group also stated that the KIGS data for children born small for gestational age was used in additional analyses, so that the ICER based on this data is also presented. See FAD sections 4.2.21 and 4.3.9.

Consultee	Comment	Response
Novo Nordisk	Please note that as of 1st January 2010 the price of Norditropin SimpleXx reduced from £21.39/mg to £21.27/mg.	The Appraisal Committee members were aware of the reduction in price of Norditropin as they received the full text of the comments from consultees and commentators and a summary of any comments received from other individuals or organisations. This follows the process outlined in section 3.5.35 in NICE's guide to the multiple technology appraisal process. As the price reduction was expected to have only a small effect on the ICERs, no updated analyses were requested. To ensure consistency throughout the FAD, no change has been made to section 3.5 as the economic analyses in the FAD are based on the original price of Norditropin.
	III. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? Yes, Novo Nordisk believes that the committee has come to a fair conclusion based on the evidence. We would also like to suggest that 2013 is too soon to consider the review of this guidance, given that the evidence base is unlikely to change significantly by such time.	Comment noted. The guidance on this technology will be considered for review in May 2013. During this period, the Institute will identify any new evidence available and trials that are due for completion. The Institute will then determine whether and when a review of the guidance should be undertaken.

Consultee	Comment	Response
Novo Nordisk	**IV. Are there any equality related issues that may need special consideration?** No We are pleased that NICE has recognised the important benefits of human growth hormone for the treatment of growth failure in children and welcome the recommendations set out in the ACD. If you have any further questions regarding our response, or any other matters please do not hesitate to contact me.	Comment noted.
Pfizer	Pfizer is pleased that the Appraisal Committee (AC) after due consideration of the evidence submitted and the views of the manufacturer consultees, commentators, clinical and patient experts has produced a positive preliminary recommendation for somatropin use in all its licensed indications. In particular, we welcome the AC comments in Section 4.3.2 on p30 that somatropin is a clinically effective treatment for children with growth failure: *"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."*	Comment noted. Comment noted

Consultee	Comment	Response
Pfizer	Pfizer also welcomes the AC conclusions in Section 4.3.11, p35 that somatropin represents a cost-effective treatment for children with growth failure associated with the conditions under consideration. *"..the Committee agreed that the ICERs for Somatropin were likely to fall within the range normally considered an acceptable use of NHS resources for all conditions under consideration. The Committee therefore concluded that within its marketing authorisation Somatropin represents a cost-effective treatment for children with growth failure associated with the conditions under consideration."*	Comment noted.
	Overall, Pfizer agrees that all the relevant evidence for somatropin has been taken into account and that the summaries of the clinical and cost effectiveness for somatropin have been interpreted in an appropriate manner within the ACD with the result that the provisional recommendations are sound and a suitable basis for guidance to the NHS.	Comment noted.

Consultee	Comment	Response
Pfizer	However, there are three aspects of the AC recommendation that need particular reconsideration and these are summarised as follows:	
	1. A lack of consistency between the information on biosimilars provided in the ACD and the prescribing guidance on biosimilar medicines provided by the MHRA and BNF, and factual inaccuracy regarding the claim of 'equivalence' between Omnitrope and Genotropin.	Comment noted. See below for response to detailed comments.
	2. An absence of an explicit recommendation for the continuation of somatropin for children who attain their target height but remain GH deficient.	Comment noted. See below for response to detailed comments.
	3. The lack of acknowledgement in the ACD regarding the value of the research evidence from Pfizer's KIGS database	Comment noted. See below for response to detailed comments.
	Finally, we have a minor comment regarding the statement included in Section 4.2.5, p22 of the ACD stating that the manufacturers economic model was "based on the model for NICE Technology Appraisal guidance 42 but was extended to consider longer-term outcomes to estimate cost effectiveness in terms of cost per QALY (rather than per cm of height) gained." This statement is not correct as the Pfizer model was a completely new model developed for the re-review appraisal as it was based on a cost per QALY analysis.	Comment noted. FAD section 4.2.5 has been amended.

Consultee	Comment	Response
Pfizer	1. A lack of consistency between the information on biosimilars provided in the ACD and the prescribing guidance on biosimilar medicines provided by the MHRA and BNF, and factual inaccuracy regarding the claim of 'equivalence' between Omnitrope and Genotropin. Pfizer welcomes reference in the ACD to the special circumstances relating to biosimilar medicines. As the AC notes, biosimilar medicines have been licensed by the European and UK regulatory agencies, however several additional pieces of guidance have been put in place to ensure that effective arrangements for pharmacoviligance are maintained and that prescribing of biosimilar medicines occurs in a safe manner. We note that although the wording used in the ACD is based upon guidance provided by British National Formulary (BNF) and Medicines and Healthcare Products Regulatory Agency (MHRA), it does not reference this guidance in full. In so doing, we are concerned that the ACD does not fully explain the significance of the recommendation to prescribe biotechnology medicines by brand-name: to ensure appropriate adverse event reporting and to prevent inappropriate substitution of non-equivalent medicines.	Comment noted See below for response to detailed comments. Comment noted. Comment noted.FAD section 3.2 has been amended to include the advice given in the British National Formulary regarding the prescribing of biosimilar products by brand-name.

Consultee	Comment	Response
Pfizer	In order to ensure consistency, we would recommend wording that exactly reflects the guidance provided by the BNF and MHRA in the appropriate section of the BNF 'General Guidance' on biosimilar medicines http://bnf.org/bnf/bnf/58/29404.htm#_200789 and to the more detailed information provided in the MHRA Drug Safety Update of February 2008 http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON2033917 We would suggest replacing the abbreviated information provided in Section 3.1 of the ACD, footnote 1, p9, with the full advice of the BNF (page 9): *"A biosimilar medicine 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. Biosimilar medicines have black triangle status at the time of initial marketing. It is important to report suspected adverse reactions to biosimilar medicines using the Yellow Card Scheme (see Adverse Reactions to Drugs). For biosimilar medicines, adverse reaction reports should clearly state the brand name of the suspected medicine".*	Comment noted. FAD section 3.2 has been amended to include the advice given in the British National Formulary regarding the prescribing of biosimilar products by brand-name.

Consultee	Comment	Response
Pfizer	Likewise, we would suggest that the wording included in Section 4.3.5 of the ACD, p31 should be amended to more closely reflect the advice of the BNF and MHRA as stated previously above. Finally, Section 4.3.6, p31/32 contains factual inaccuracy with respect to the biosimilar Omnitrope. The section states that: "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 European Medicines Agency (EMEA) and that the studies had provided evidence on the equivalence of the two products". Although the manufacturer of the biosimilar product has undertaken trials as part of its regulatory submission to the EMEA, these studies can only be said to demonstrate 'clinical comparability', not 'equivalence'. The nature of biotechnology medicines means that it is inaccurate and misleading to state that the trials provide evidence of equivalence of the two products (Mellstedt et al 2008). Furthermore, the Appraisal Committee should note that the clinical development programme for Omnitrope did not conduct head to head trials between the marketed version of Omnitrope and Genotropin, as only an earlier development version of the biosimilar product (Omnitrope - Covance) was studied against Genotropin (Omnitrope EPAR).	Comment noted. The consideration of the evidence section has been amended to provide greater clarification on the manufacturing process and regulatory environment of 'biosimilar' products. See FAD section 4.3.4. Comment noted. .

Consultee	Comment	Response
Pfizer	2. **An absence of an explicit recommendation for the continuation of somatropin for children who attain their target height but remain GH deficient.** Pfizer notes that although the AC in Section 1 of the ACD includes specific wording regarding the reasons for discontinuation of somatropin treatment, it is not clear what explicit recommendation has been made for those children who attain their target height but remain GH deficit. In this group of patients, the assessment group has demonstrated that somatropin is clinically and cost-effective at a cost per QALY below £30k. Therefore, we would suggest that wording is added to Section 1 of the ACD to reflect the clinical importance of continuing somatropin treatment in patients who remain GH deficit after reaching their target height.	Comment noted. The scope defines the population as 'Children and young people for whom human growth hormone is initiated for the purpose of maximising height potential and body composition and whose growth is affected by growth hormone deficiency, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age or SHOX deficiency. Therefore no explicit recommendation has been included in the FAD for those children who attain their target height but remain growth hormone deficit. However recommendation 1.3 and section 4.3.14 states that treatment should not be discontinued by default and that the decision to stop treatment should be made in consultation with the patient and/or carers.

Consultee	Comment	Response
Pfizer	3. The lack of acknowledgement in the ACD regarding the value of the research evidence from Pfizer's KIGS database We note in Section 4.3.10 of the ACD that the AC in considering the clinical evidence for somatropin therapy has concluded that the source of clinical effectiveness irrespective of whether its obtained from RCTs or the KIGS database did not affect the magnitude of the Assessment Group's estimates for the majority of the conditions. However, this conclusion fails to recognise the true value of the research evidence for somatropin from the KIGS database in terms of complementing the information from published registered clinical trials, providing evidence in the absence of RCT data and informing clinicians regarding the real world effectiveness of somatropin treatment. Therefore, we would suggest that the AC include the following additional wording within the ACD that is consistent with that included in Section 4.3.2, p8 of the previously published NICE technology appraisal guidance 42(TA42): *"In its consideration the Committee recognised the value of research evidence from both RCT and observational sources, including the KIMS/KIGS (Pharmacia International Metabolic and Growth Databases) and similar databases."*	Comment noted. The considerations section needs to focus on the rationale behind the decision taken by the Committee.
Sandoz	Sandoz UK welcomes the opportunity to comment on the appraisal consultation document (ACD) that sets out the Appraisal Committee's (AC's) recommendations on human growth hormone (somatropin) for the treatment of growth failure in children. We welcome the Institute's broad recommendations	Comment noted.

Consultee	Comment	Response
Sandoz	We have a significant area of concern relating to the implied safety issues alluded to in the ACD, and relating to our product Omnitrope, which is a biosimilar preparation. At paragraph 4.3.5, the AC notes that "biosimilar drugs may have a different safety profile…because different cell lines and differences in the fermentation and purification processes used in the manufacturing process may lead to different immunological effects". There is no evidence for this statement and, indeed, there is a growing body of data to suggest the opposite position is true. While there may be slight variations in the Omnitrope manufacturing process, these differences exist across all products available in the UK, and there is no evidence to suggest this will result in a different immunological profile. The basic fermentation process is similar, and the final product is stringently tested to ensure its similarity to the originator Genotropin. Furthermore Omnitrope manufacturing process conforms to the highest Sandoz / Novartis quality standards, fully reviewed, and subsequently approved for use by the EMEA. We have provided further details on this below.	Comment noted. The consideration of the evidence section has been amended to provide greater clarification on the manufacturing process and regulatory environment of 'biosimilar' products. See FAD section 4.3.4.
	The Committee notes that making specific recommendations around the safety of a drug is outside its remit. This is, of course, correct and given that there is no evidence to show increased safety issues around Omnitrope compared to other growth hormones available in the UK, there should be no allusion to such in the guidance. Later in paragraph 4.3.6, it is, in any case, acknowledged by clinical specialists and patient experts that they "were not aware of any differences in the products available in terms of safety and efficacy". This is surely sufficient statement on the matter.	Comment noted. 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. See FAD section 4.3.4.

Consultee	Comment	Response
Sandoz	We believe that perceived concerns around safety are reflected in the way in which the appraisal committee has made its recommendations. Specifically, we note at paragraph 1.2 that the recommendations are that “the choice of product should be made on an individual basis after informed discussion ... about the advantages and disadvantages of the products available”. Only after that consideration does acquisition cost enter consideration on the basis of these recommendations. This is an unusual form of wording for the AC to use. Indeed we could find only one other instance of a TAG where anything approaching this wording has been used. In general, NICE’s recommendation, where there are no differences between products, is to use the therapy with the lowest acquisition cost. Since we would argue that there are no other differences between the products in this instance, and for consistency, we believe that this is how the guidance should read, without qualification. The statement at the end of paragraph 4.3.11 is perhaps a more sensible way of expressing the recommendation	Comment noted. The Committee agreed that patient choice is an important factor in maximising adherence to therapy. It therefore concluded that the least costly product that meets the need of the individual child and maximises the likelihood of adherence to treatment should be chosen. See FAD sections 1.2, 4.3.5 and 4.3.13.

Consultee	Comment	Response
Sandoz	We are aware of no evidence that could credibly support any finding or suggestion that Omnitrope is less safe and effective than their originator counterparts. Sandoz now has 84 months of safety & efficacy data on Omnitrope, as our product has been extensively used throughout the world. This data demonstrates in this long term study that there were no unknown safety issues around the product. This data is presented in a recent study by Romer et al that analysed safety data in children over a seven year timeframe. It concluded both that there was clinical comparability between Omnitrope and Genotropin and that Omnitrope was well tolerated and showed no major difference in safety. Sandoz is not aware of any evidence to the contrary. Sandoz also maintains its own register of patients from which we are collecting data. This contains 300 patients from across Europe. We are now increasing patient numbers in this database to include more patients from the UK, highlighting our ongoing commitment	Comment noted.
	The concern has been raised during this appraisal around the theoretical possibility of biosimilars provoking an immune response. It should be noted that most recombinant human growth hormones (rhGH) are produced by batch growth of recombinant E.coli with appropriate plasmid(s), and the downstream processing is virtually identical. This being the case then Omnitrope, being biosimilar, is the same as the other reference rhGHs produced. Any immunogenicity potential would, therefore, apply to all of them and not specifically to a biosimilar.	Comment noted. The Committee heard that the of different fermentation and purification processes used by the manufacturers of the 'biosimilar' product and the originator biopharmaceutical product may lead to different immunological effects. Therefore 'biosimilar' products may have a different safety profile from the originator biopharmaceutical product. However 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. See FAD section 4.3.4.

Consultee	Comment	Response
Sandoz	The licensing process for biosimilars is as rigorous in every way as that for the originator reference medicine. CHMP has developed specific guidelines for them, which encompass overarching guidelines, general guidelines on quality, non-clinical and clinical issues, and class-specific guidelines focusing on recombinant human erythropoietin, granulocyte colony-stimulating factor, human insulin and growth hormone (GH). Importantly, these guidelines state that 'comparability studies will be needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy'. In short, European licensing provisions require biosimilars to be assessed according to regulatory criteria that are just as stringent as those for original biological products. Furthermore, Omnitrope is manufactured in a modern facility in Austria, owned by Novartis / Sandoz, which manufactures 20 originator products and is exposed with equal rigour to inspections by authorities.	Comment noted.

Consultee	Comment	Response
Sandoz	A great deal of - often mischievous - mythology has been spun around biosimilars, implying that licensing and manufacturing processes for these drugs are in some way sub-standard. This is categorically not the case. Given the complexity of biologics, it is impossible to refer to these molecules in terms of being identical, since even different batches of the same biological product will vary regarding the active substance (for example, between two batches of Genotropin or between two batches of Omnitrope) – hence their being called biosimilars and not generics or biogenerics. This has been fully acknowledged by the European Medicines Evaluation Agency (EMEA). In the USA and Japan they are called follow-on protein products and, in Canada, subsequent entry biologics.	Comment noted.
	Sandoz is very clear that our biosimilar products do offer very real benefits over other therapies in this disease area, in the form of reduced costs and improved access to treatment, whilst maintaining the highest standard of patient care. Along with Genotropin, Omnitrope is the only product licensed for all the main indications (including PWS not SHOX) and is approximately 21% less expensive at list price.	Comment noted.

Consultee	Comment	Response
Sandoz	In paragraph 4.3.6, the AC notes that the choice of product depends in part on the choice of delivery system and the support package offered by the manufacturer. We would just wish to note that Sandoz offers the same level of care and the same support package as is provided with the other products. We would ask, in preparing the final appraisal determination, that the AC pays particular attention to any statements that might appear to imply the Omnitrope is less safe than the other treatments. Clinicians and patients may well choose different remedies based on different factors but there should be no question of safety being an issue with our product and this should not be a reason why individuals would choose not to use it. We would ask that the Institute's final guidance is clear on that point	Comment noted. Comment noted. The Committee was aware that making specific recommendations around the safety of a drug was outside the remit of NICE, and based on the marketing authorisation for Omnitrope, it was satisfied that it could consider Omnitrope for the treatment of growth failure alongside the other six somatropin products. See FAD section 4.3.4.
British Society for Paediatric Endocrinology and Diabetes (BSPED)	Many thanks for asking the British Society for Paediatric Endocrinology and Diabetes (BSPED) to comment on the Health Technology Appraisal of Human Growth Hormone for the treatment growth failure in children (review) Appraisal Consultation Document. In general the BSPED are quite happy with the document and only have one or two minor points to make, detailed below. We also recognise the almost universal lack of health-related quality of life data and support the Committee's recommendation that this be addressed in planned research projects across the spectrum of growth hormone prescribing for children (section 6.2). There is currently a UK cohort study examining health related QoL in families prescribed GH for GHD and Turner syndrome but results are not expected until end of 2010.	Comment noted. This study is referred to in FAD Section 6.1.

Consultee	Comment	Response
British Society for Paediatric Endocrinology and Diabetes (BSPED)	Comments: Numbered according to the ACD 1.2 Add…The decision to initiate somatropin should be made by a paediatrician with a specialist expertise in growth hormone disorders (paediatric endocrinologist). This should ally with section 4.3.4 where the wording should state in the last line '.. a physician with specialist experience in growth hormone disorders (endocrinologist).	Comment noted The recommendations in the FAD have been amended to provide greater clarification on which physicians should initiate somatropin treatment. See FAD section 1.2. Comment noted. The consideration of the evidence section 4 has been amended to provide greater clarification on which physicians should be involved in the decision discontinue somatropin treatment after attainment of final height. See FAD section 4.3.14.

Consultee	Comment	Response
British Society for Paediatric Endocrinology and Diabetes (BSPED)	1.3: The wording in this section is different from section 4.3.4. Also it does not clarify what should happen at transition of patients with GHD. The BSPED would recommend changing the wording in section 1.3 to: Treatment with somatropin should be discontinued if any of the following apply: • *there is an increase in growth velocity of 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* *Once final height is obtained, treatment should be discontinued only after consultation with patients and/or their carers by a paediatrician with specialist expertise in the management of growth hormone disorders or by an endocrinologist with specialist expertise in the management of growth hormone treatment in adults.* This fits better with section 4.3.4 which states: *This guidance recommended that treatment with somatropin should be discontinued if: there is an increase in growth velocity of 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, or there are insurmountable problems with adherence.*	Comment noted. The recommendations in the FAD have been amended to provide greater clarification on what should happen to patients during the transition of care between paediatric and adult services. See FAD sections 1.3 and 4.3.14.

Consultee	Comment	Response
British Society for Paediatric Endocrinology and Diabetes (BSPED)	2.5: should say …below the 2nd percentile for height within their first year and remain so throughout childhood on account of more pronounced deceleration in height velocity.	Comment noted. FAD section 2.5 has been amended.
	2.6: The international consensus definition of SGA is below -2 SD for birth weight or length.	Comment noted. FAD section 2.6 has been amended.
	2.8: ….oxandrolone may be added… The BSPED UK Turner study has demonstrated a positive effect of adjuvant therapy with oxandrolone with growth hormone on final height. This data has been presented at various national and international meetings and is in preparation for publication	Comment noted. Adjuvant therapy with oxandrolone is outside the scope of this appraisal. The Institute recognises that oxanadrolone may be added to growth hormone treatment. See FAD section 2.8.
	3.3: You have expressed all the doses/kg as mcg/kg/day apart from SHOX deficiency which you have expressed as mg/kg/day. Probably better to keep the same format throughout and therefore SHOX should be 45-50mcg/kg daily.	Comment noted. FAD section 3.3 has been amended.
	3.4: The way this paragraph is written suggests that leukaemia is a possible side effect of treating children with GH deficiency with GH. This is not the case and there is no evidence for this. This was based on very old Japanese data which suggested an increased risk of leukaemia relapse in children treated with GH who had previously been treated for leukaemia. This study has never been substantiated in other parts of the world or from the long term post marketing surveillance data. The BSPED feel this sentence should be removed.	Comment noted. FAD section 3.4 has been amended.

Consultee	Comment	Response
British Society for Paediatric Endocrinology and Diabetes (BSPED)	4.3.3: Somatropin treatment can therefore play a major role in improving quality of life and may also improve long term cardiovascular health and reduce the risk of diabetes even after discontinuation of treatment. 4.3.4: See note above in relation to 1.2. 4.3.11: last sentence the least costly product that meets the needs of the individual patient and maximises the likelihood of adherence to treatment should be chosen when more than one product is suitable following patient choice. 6.1: 3rd bullet point. There is a controlled cohort study…	Comment noted. FAD section 4.3.3 has been amended. Comment noted. Comment noted. The Committee agreed thatt patient choice is an important factor in maximising adherence to therapy. It therefore concluded that the least costly product that meets the need of the individual child and maximises the likelihood of adherence to treatment should be chosen. See FAD sections 1.2, 4.3.5 and 4.3.13. Comment noted. FAD section 6.1 has been amended.
Royal College of Nursing	Nurses working in this area have reviewed the Appraisal Consultation Document for the health technology appraisal of human growth hormone for the treatment of growth failure in children. There are no comments to make on this document at this stage.	Comment noted.

Consultee	Comment	Response
Royal College of Paediatrics and Child Health	**Has all of the relevant evidence been taken into account?** The College is not aware of further relevant published material which should be taken into account. However, we note that much of the evidence cited for the appraisal document was of rather poor quality. There were two main areas of difficulty: 1. The studies used to appraise the use of human growth hormone (HGH) in small for gestation age (SGA) infants used HGH in doses which exceeded UK licensed doses. Clinical experience suggests that higher doses produce faster growth. If UK licensing is upheld, poorer height velocities may result. 2. There was little data on the effect of HGH on the Quality of Life. There is a national multi-centre study (supported by the British Society for Paediatric Endocrinology and Diabetes) currently in progress in the UK which should add to this evidence base considerably. It seems rather odd that this appraisal consultation document has been drafted before the results of this study are known.	Comment noted. See below for responses to detailed comments. Comment noted. The Committee noted that the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources. However, the Committee concluded that the source of the clinical effectiveness data did not affect the magnitude of the Assessment Group's cost effectiveness estimates for the majority of the conditions. See FAD section 4.3.9. Comment noted. The guidance on this technology will be considered for review in May 2013. During this period, the Institute will identify any new evidence available and trials that are due for completion. The Institute will then determine whether and when a review of the guidance should be undertaken.

Consultee	Comment	Response
Royal College of Paediatrics and Child Health	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The College thinks that the provisional recommendations of the Appraisal Committee seem generally sound. Hopefully, the findings will give further support to the cost-effectiveness of HGH treatment in its current clinical use.	Comment noted.
	The College is concerned about the advice to use the HGH products with the lowest acquisition costs where possible. Anecdotal evidence shows that allowing patients to choose their preferred HGH device improves adherence. Although most HGH products are biochemically identical, different injection devices and home care packages result in important distinctions between products. We note that biosimilar products such as Omnitrope have not had widespread clinical usage. We recommend that these cheaper products may be offered to patients but not encouraged over their more conventional expensive counterparts.	Comment noted. The Committee agreed that t patient choice is an important factor in maximising adherence to therapy. It therefore concluded that the least costly product that meets the need of the individual child and maximises the likelihood of adherence to treatment should be chosen. See FAD sections 1.2, 4.3.5 and 4.3.13.

Consultee	Comment	Response
Royal College of Paediatrics and Child Health	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** The College notes that individuals with Prader Willi syndrome have learning difficulties and the indications for the use of HGH treatment in this condition are more complex than for height gain alone, with more subtle outcomes. The evidence base for the effectiveness of HGH treatment in this condition is rather thin. It is important that careful consideration is given to any recommendations made for this group in view of these complexities.	Comment noted. The Committee considered that the ICER for Prader–Willi syndrome was likely to be considerably lower than that derived from the Assessment Group's analysis because of the underestimation of the true utility gain. The Committee did not consider that a change in the recommendation made in TA 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. See FAD sections 4.3.8, 4.3.11 and 4.3.13.

Consultee	Comment	Response
Commissioning Support Appraisals Service	Here is the response from CSAS to the review of NICE TAG 42 on Growth Failure in Children on behalf of NHS Birmingham East and North – NHS BEN (which replaced NHS Wirral as consultee). **Headline response** There is insufficient evidence of cost-effectiveness to justify the use of growth hormone in children with any of the conditions listed – with the exception of demonstrated growth hormone insufficiency. **Summary** In the TAR base case only the use of somatropin for growth failure associated specifically with growth hormone deficiency achieved an ICER of less than £30,000 per QALY. Somatropin use for growth failure in other conditions arrived at ICERs of more than £30,000 per QALY in the base cases. Even after reductions in BNF prices were taken into account for the ACD, the ICERs were still greater than £30,000 for all conditions apart from growth hormone deficiency and the actual evidence of clinical benefit (particularly of improvements in quality of life associated with TREATMENT) was too limited to justify any increase in the ICERs.	Comment noted. Comment noted See below for response to detailed comments. Comment noted. The Committee agreed that that there was uncertainty about the utility values used in the models. The Committee concluded 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. See FAD sections 4.3.7, 4.3.8, 4.3.10, 4.3.11, 4.3.13. .

Consultee	Comment	Response
Commissioning Support Appraisals Service	for patients small for gestational age, did not use doses of growth hormone licensed in the UK. It would therefore not be appropriate to use these studies to make recommendations based upon use of growth hormone within its licence	Comment noted. The Committee noted that the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources. However, the Committee concluded that the source of the clinical effectiveness data did not affect the magnitude of the Assessment Group's cost effectiveness estimates for the majority of the conditions. See FAD section 4.3. 9.

Consultee	Comment	Response
Commissioning Support Appraisals Service	Although the Appraisal Committee considered that the full disutility associated with growth failure and full utility gain from somatropin treatment had not been captured in these analyses, this does not appear to be based on actual studies of change in utility associated with the sort of likely gain in final adult height (3.3cm) due to treatment, as estimated by some studies. Furthermore, there was limited evidence of the impact of growth hormone treatment on final adult height and a lack of direct evidence demonstrating the impact of height increase due to growth hormone treatment on quality of life in childhood. We note the comments by other consultees, particularly the British Society for Paediatric Endocrinology and Diabetes (BSPED), the Royal College of Paediatrics and Child Health (RCPCH), and the Royal College of Physicians, and we agree that the evidence of clinical effectiveness of growth hormone in most conditions (particularly Small for Gestational Age) does not demonstrate that treatment with growth hormone produces worthwhile improvements in quality of life. Similarly, we agree that there are too many inappropriate assumptions contained within the economic models – particularly regarding the values attributed to quality of life associated with the estimate minimal increase in final adult height. This is particularly important in patients whose only diagnosis is “small for gestational age”, which is an epidemiological definition based on the position of the patient’s height within a normal distribution, and where there is limited evidence of the impact of treatment on final adult height and no direct evidence of improvements in quality of life associated with treatment-associated height gain.	Commented noted.

Consultee	Comment	Response
Commissioning Support Appraisals Service	CSAS and NHS BEN note that the studies that examined growth hormone treatment for patients small for gestational age, did not use doses of growth hormone licensed in the UK. It would therefore not be appropriate to use these studies to make recommendations based upon use of growth hormone within its licence.	Comment noted. The Committee noted that the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources. However, the Committee concluded that the source of the clinical effectiveness data did not affect the magnitude of the Assessment Group's cost effectiveness estimates for the majority of the conditions. See FAD section 4.3.9.

Consultee	Comment	Response
Department of Health	We are not certain as to which children, born small for gestational age, should be offered somatropin as a treatment option:	Comment noted. See below for response to detailed comments
	In 1.1, the committee recommends somatropin (GH) as a treatment option in children with the following condition - being born small for gestational age (SGA) - but that term does not appear to be specifically defined.	Comment noted. The Institute appraises all technologies within the therapeutic indications specified in the marketing authorisation. The recommendations in the FAD have been amended to provide greater clarification on the definition of being born small for gestational age. See FAD section 1.1.
	In 2.6, various thresholds for SGA are mentioned.	Comment noted. FAD section 2.6 had been amended to include the International consensus definition of born small for gestational age and the licensed indication for somatropin.
	In 4.1.21, we are unable to identify RCTs that met the criteria for the use of GH, as prescribed in the licence for GH in children born SGA. We would be grateful for clarification.	Comment noted. The Assessment Group could not identify any RCTs whose inclusion criteria matched those specified in the licensed indication. Therefore, the Assessment Group amended the criteria to be "growth disturbance (current HtSDS <-2.5, but with no reference to parental height) in short children born small for gestational age with a birth weight and/or length below -2SD, who failed to show catch-up growth (with no particular criteria specified) by 3 years of age or later.". See section 3.7.1, page 72 of the Assessment Report prepared by Southampton Technology Assessment Centre.

Consultee	Comment	Response
Department of Health	In 4.2.17, the cost per cm in the SGA group is substantially higher than other conditions, accepting that there are other cost calculations. In our view, there is a need to be very precise about which children should be offered such a treatment need to be very precise about which children should be offered such a treatment option. If this is within the licensed indications, we feel that this should be clearly stated from the outset. We are aware that a huge proportion of paediatric medicines are prescribed by paediatricians off licence. We are also aware of the variability of access to medicines around the country. We believe that the recommendations to the NHS should be more precise and clear, in order to prevent both inequity in access and inappropriate treatment of children	Comment noted. The Institute appraises all technologies within the therapeutic indications specified in the marketing authorisation. The recommendations in the FAD have been amended to provide greater clarification on the definition of being born small for gestational age. See FAD section 1.1.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above consultation. We have no comments to make at this stage.	Comment noted

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical Specialist, NHS Quality Improvement Scotland	Overall I believe that the recommendations are reasonable, appropriate and pragmatic given 1) the relative lack of high quality relevant evidence, 2) the difficulty in determining effects on the clinically most relevant outcomes – and, therefore, 3) the major assumptions that have to be made about what constitutes 'effectiveness', and thus 'cost-effectiveness' and cost per QALY, but 4) the clinical value placed by patients and their representatives on the benefits of treatment with somatropin for growth failure, and which are poorly captured by the extant studies.	Comment noted.
	I would like to see a further recommendation that there should be 'compulsory' post-marketing surveillance of all patients treated, at whatever age and for whatever indication, with somatropin. This should be a joint responsibility of manufacturers and clinicians (through the British Society for Paediatric Endocrinology and Diabetes and the Society for Endocrinology) and should, in particular, be extended to the surveillance of adults no longer treated with somatropin but who were treated as children and/or adolescents. This is important for all brands of somatropin and particularly so for Omnitrope, the 'biosimilar' preparation where the medium- and long-term safety profile is less clear.	Comment noted. Making specific recommendations regarding the safety of a drug is s outside the remit of NICE. See FAD section 4.3.4.

Nominating organisation	Comment	Response
Patient Expert, Turner Syndrome Support Society (TSSS)	Thank you for sending a copy of the above document to the TSSS and for the invitation to comment on it. You specify four headings initially on which we should comment. We will restrict our comments in the main to Turner Syndrome. i) **Do you consider that all of the relevant evidence has been taken into account?** The analysis is very extensive and we are sure that as far as is possible you have used all available published evidence.	Comment noted. Comment noted.

Nominating organisation	Comment	Response
Patient Expert, Turner Syndrome Support Society (TSSS)	**ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** The summary of clinical effectiveness was as expected and clearly in Turner Syndrome the use of GH is effective. The summary of cost effectiveness was also very acceptable to us but there were wildly varying costs in relation to centimeter of final height gained or in relation to QALY. See paragraphs 4.2.1, 4.2.2, 4.29, 4.2.10, 4.2.17, 4.2.18. These variations were seen in absolute cost or relative cost (when compared to growth hormone deficiency). As an example of the variation relative cost per centimeter were from x 2 to x 4.5 approximately. Different data sets and methodologies generate these variations. We think a reasonable summary would be that it costs about twice as much per extra centimeter of final or adult height when treating a girl with Turner Syndrome compared to a child with growth hormone deficiency, not a surprising ratio considering the comparison of an individual who is GH replete to one who is deficient. We very much agree with the Committee who state in paragraph 4.3.8 that the utility estimates, "may not capture the potential increased utility from normal height gain during childhood".	Comment noted.

Nominating organisation	Comment	Response
Patient Expert, Turner Syndrome Support Society (TSSS)	**iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** Yes	Comment noted.
	iv) Are there any equality related issues that may need special consideration? No.	Comment noted.
	You asked for comment on the proposed date for review of guidance, namely May 2013. In our opinion this is rather early. The committee has made some suggestions for more research and it is highly unlikely that such research in the field of growth could be completed within that time frame. We would suggest 2018 at the earliest. In conclusion, we would like to express our gratitude to the Committee for the very thorough analysis that it has conducted and for continuing to support the use of GH for girls with Turner Syndrome. We are also grateful that our observations have been acknowledged and understood by the Committee.	Comment noted. The guidance on this technology will be considered for review in May 2013. During this period, the Institute will identify any new evidence available and trials that are due for completion. The Institute will then determine whether and when a review of the guidance should be undertaken.

Comments received from commentators

Commentator	Comment	Response
NHS Quality Improvement Scotland (NHS QIS)	1. **Whether you consider that all the relevant evidence has been taken into account**.	
	I think all relevant evidence has been taken into account.	Comment noted.
	2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.	
	Yes they are. There needs to be a greater amount of data for evaluating change in quality of life following treatment with somatropin. Results from some ongoing studies shall be available before 2013 and will need to be carefully assessed.	Comment noted.
	3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	
	Yes they are.	Comment noted.

Commentator	Comment	Response
Southampton Health Technology Assessments Centre (SHTAC) University of Southampton	The team here has no particular comments on the document, but spotted a couple of small typos: 4.2.4: "which assumed a lifelong change in body BMI" should probably read "which assumed a lifelong change in BMI" 4.3.10: "It recognised that the source of the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources" should probably read "It recognised that the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources" 4.3.11: "It noted from a sensitivity analyses undertaken by the Assessment Group...." should be " it noted from a sensitivity analysis...."	Comment noted. Comment noted. FAD section 4.2.27 amended. Comment noted. FAD section 4.3.9 amended. Comment noted. FAD section 4.3.12 amended.

Comments received from members of the public

Role*	Section	Comment	Response
Consultant in Public Health	1	See comments on Section 4.	Comment noted.
	2	This was clear and useful in the main. The epidemiological definition of ‘small for gestational age’ is interesting and has caused much discussion and wonder whether it is appropriate to medicalise what is in essence the ‘tail’ normal distribution	Comment noted.

* When comments are submitted via the Institute’s web site, individuals are asked to identify their role by choosing from a list as follows: ‘patent’, ‘carer’, ‘general public’, ‘health professional (within NHS)’, ‘health professional (private sector)’, ‘healthcare industry (pharmaceutical)’, ‘healthcare industry’(other)’, ‘local government professional’ or, if none of these categories apply, ‘other’ with a separate box to enter a description.

Role*	Section	Comment	Response
Consultant in Public Health	3	This section is clear	Comment noted
	4	We note that the quality of evidence is poor in places, and thus were surprised that recommendations were made regarding the technologies in question.	Comment noted. The Committee noted that the clinical effectiveness data used in the manufacturers' and the Assessment Group's economic models were obtained from different sources. However, the Committee concluded that the source of the clinical effectiveness data did not affect the magnitude of the Assessment Group's cost effectiveness estimates for the majority of the conditions. See FAD section 4.3.9.
	6	Appropriate – clearly a need for further 'good quality' research and thus these are welcomed	Comment noted
	7	No comment	Comment noted
	8	Given the new research awaited and their dates for delivery – we wonder whether appropriate to bring forward the date slightly – to act on the findings if/as appropriate	Comment noted. The guidance on this technology will be considered for review in May 2013. During this period, the Institute will identify any new evidence available and trials that are due for completion. The Institute will then determine whether and when a review of the guidance should be undertaken.