Jeremy Powell, Esq
Technology Appraisal Project Manager
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5th January 2010

Dear Mr Powell,

RE: Appraisal Consultation Document: Human growth hormone (somatropin) for the treatment of growth failure in children (review of NICE technology appraisal guidance 42)

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.

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.

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.

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.

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.

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.

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.

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.
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.

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.

Yours sincerely,

 , Sandoz UK