SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of NutropinAq. For information on changes after approval please refer to module 8.

1. Introduction

Growth hormone (GH) is a single polypeptide chain consisting of 191 amino acids, and is secreted by the anterior lobe of the pituitary gland. Secretion is under hypothalamic control via growth hormone-releasing hormone (GHRH) (stimulating secretion of GH) and somatostatin (inhibiting secretion of GH). Circulating levels of GH varies greatly through the day with very low levels through most of the day and short spikes of high concentration occurring primarily during sleep or after exercise or meals.

GH secretion varies greatly through life, with secretion being low during infancy, increasing during childhood and peaking during puberty. In adults above 30, secretion gradually decreases. GH is necessary for normal longitudinal growth. Thus, GH deficiency in childhood leads to short stature.

The effect of GH is primarily mediated by the GH induced secretion of other hormones known as somatomedins or insulin-like growth factors (IGF) (of which IGF-1 is considered the most important) which then directly stimulates growth of both bone and several organs. In contrast to GH levels, circulating levels of IGF-1 remains relative stable throughout the day. In addition to its effect on growth, GH has pronounced effect on lipid, protein and carbohydrate metabolism. GH causes lipolysis and stimulates amino acid incorporation into muscle protein. The action of carbohydrate metabolism is complex. GH has an agonistic effect on insulin secretion but and antagonistic effect on the peripheral action of insulin.

As mentioned above GH deficiency (either ideopathic or secondary to tumours, irradiation, trauma or infection in the pituitary gland/hypothalamic area) in children leads to impairment of growth and eventually to short stature. In adults, GH deficiency contributes to decrease in muscle strength as well as change in body composition, especially increased fat mass and decreased lean body mass. GH deficiency in adults has also been reported to be associated with reduced psychological well-being and reduced quality of life. Previous studies have demonstrated that administration of exogenous human growth hormone can partially restore normal growth in growth hormone deficient children. Furthermore, administration of exogenous human growth hormone may lead to reduction in fat mass, increase in muscle mass and may counteract lack of energy.

Children with renal insufficiency or Turner's syndrome generally have impaired growth. Although this growth impairment is not due to an absolute GH deficiency, previous studies have shown that treatment with exogenous GH can partially restore normal growth in these patients.

NutropinAq is a product containing recombinant human growth hormone (rhGH). produced by recombinant DNA technology in a genetically modified E.coli. The recombinant hormone is secreted as a fusion protein containing a 23 amino acid signal peptide in front of the somatropin. This signal peptide causes the protein to be secreted into the periplasm of the E.coli where the signal peptide is cleaved from the growth hormone (somatropin). The amino acid sequence of the product is identical to that of the natural human growth hormone.

NutropinAq is a sterile ready-to-use aqueous solution containing 5.0 mg somatropin per ml. Each vial contains 2 ml of solution for subcutaneous administration.

NutropinAq is indicated for:
- Long-term treatment of children with growth failure due to inadequate endogenous growth hormone secretion,
- Long-term treatment of growth failure associated with Turner syndrome,

- Treatment of prepubertal children with growth failure associated with chronic renal insufficiency up to the time of renal transplantation,
- Replacement of endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult-onset etiology. Growth hormone deficiency should be confirmed appropriately prior to treatment

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The finished product contains the following excipients: somatropin, sodium chloride, liquefied phenol, polysorbate, sodium citrate dihydrate, citric acid, water for injection.
NutropinAq is presented in glass vials closed with a rubber stopper and a flip-off cap. Each vial contains an overage of 0.2 ml of product to ensure delivery of 2.0 ml of solution.

Active substance

Development Genetics
The host cell is an *E.coli* derivative. The host cell mutations have been introduced to improve the production process. The recombinant hormone is secreted as a fusion protein containing a 23 amino acid signal peptide in front of the somatropin. This signal peptide causes the protein to be secreted into the periplasm of the E.coli where the signal peptide is cleaved from the growth hormone (somatropin). The amino acid sequence of the product is identical to that of the natural human growth hormone.

Host strain and production strain have been stability tested to verify absence of mutations.

Somatropin bulk solution appears as monograph No. 950 in the European Pharmacopoeia, an updated version of which came into force on 1st January 2000. The finished product specification complies with the requirements of the Ph.Eur.

Cell bank system
Up to 1998, stock culture vials were used to manufacture somatropin. In 1998 a switch was made and one batch of such stock culture was taken and designated master cell bank (MCB). A new working cell bank (WCB) was created from liquid nitrogen stored MCB. Either the MCB or WCB may be used for production.
The MCB has been fully characterised using adequate tests. Testing of the WCB is somewhat less than that for the MCB. Regular testing of both banks consists of viability monitoring. The cell bank is considered to have shown no change in viability upon storage at -60°C or below. Stability testing of the WCB will occur regularly. MCB testing occurs when a new WCB is prepared. Stability protocols for both the MCB and the WCB have been provided.

Fermentation and harvesting
An updated process description has been provided. Agitation rate, temperature, vessel pressure, aeration rate and pH are strictly controlled throughout the process. In-process samples are taken to ensure culture purity and a satisfactory cell density.

Purification
The production of the active substance has been adequately described. It involves the following process steps: propagation, fermentation, harvesting and purification. Somatropin is secreted into the periplasm from which release is achieved through a series of steps involving freezing, thawing and suspension. The somatropin is isolated and purified by standard chromatographic separation techniques through a series of steps. Typical elution profiles for each of the purification steps are provided.

Impurities
Potential process related impurities which may occur are *E-coli* proteins, endotoxins, host cell DNA, bacteriophage and non-host cell contamination (bioburden). Bacteriophage has not been found to date.

Based on DNA clearance studies, the amount of DNA in the finished product is calculated and found to be substantially below the WHO acceptance limit.

Characterisation
Somatropin is a single chain protein of 191 amino acids including 4 cysteine residues present as two intrachain disulphides. The observed mass is 22,125 daltons.

Primary structure has been elucidated using sequence analyses techniques. Results confirm agreement with the predicted cDNA sequence and identicality with natural human pituitary growth hormone. Secondary and tertiary structure have been confirmed. Physico-chemical characteristics have been investigated.

The results presented show no detectable structural differences between the batches studied. The results also confirm that there are no differences in impurity pattern between the batches tested.

Post-translational modifications
Potential impurities arising at the transcription or translation phases are derivatives with modified secondary and/or tertiary structure, those with modified amino acid sequence, Nor-leucine variant and high molecular weight species. Of this group of impurities, only the Nor-leucine and higher molecular weight species have been found to date.

Analytical development and process validation
The stability of the used reference standard has been monitored and recently confirmed.

The requirements of the Note for Guidance on Validation of Analytical Procedures (CPMP/ICH/281/95) are met. As raw material somatropin is basically a bulk solution of finished product, the methods used for testing of drug substance are equally valid for finished product.

Validation data of all relevant methods used during development and characterisation of the MCB have been presented.

Data have been provided for validation of the harvesting/isolation, initial and final purification processes, through formulation and dilution steps to final vial lots. Critical operational parameters have been identified and reviewed at all relevant steps. Results show that parameters were within established ranges and in-process tests conform to the test parameters. NutropinAq batches for the European market will meet the required Ph.Eur. specification.

Validation of the fermentation process has been demonstrated. Data are provided showing that the operating parameters in the fermentation process are controlled and reproducible resulting in consistency in growth profile and somatropin production.

Clearance of *E.coli* protein (ECP) contaminants has been examined at each step in the purification process. On the basis of the data presented, there is good justification for annual testing.

Batch analysis
Lists have been provided of batches used in preclinical and clinical trial. Results are provided for diffent lots of filtered formulated bulk solution manufactured at full scale. (These lots have been used in process validation studies). The batches comply with the proposed specifications.

Other ingredients

Sodium chloride is used to improve the solubility of somatropin and also to prevent development of globules and enable adjustment tonicity of the product. Polysorbate 20 is present to reduce the aggregation tendency of somatropin in solution. Citrate buffer was selected to maintain a pH of 6, thereby reducing the formation of deamidated protein whilst maintaining an adequate solubility.

Citrate buffer was chosen based on longer term visual clarity results. Peroxide levels in polysorbate 20 is controlled and the peroxide determination method presented. Phenol was chosen as a preservative as it proved to be compatible with both somatropin and the other excipients. The applicant provides antimicrobial preservative efficacy data for product preserved with phenol. All excipients comply with Ph.Eur. and USP specifications apart from liquefied phenol which is USP standard. The specification for liquefied phenol has been provided together with test methodologies.

Product development and finished product

- Method of preparation

As somatropin is not isolated during production, the active drug substance consists of a bulk formulated solution. Bulk formulated somatropin solution is weighed, filtered and stored for up to 21 days at 2-8°C prior to filling. When the total amount of bulk solution required for filling is determined, filtered bulks are pooled as necessary, and the solution sterilised by filtration. Different filter sizes are used to match flexibility in size of filling vessels and bulk material to be processed.

Solution is then filled aseptically into sterile vials, the vials sealed and stored inverted at 2-8°C. After labelling and packaging, vials are again stored at 2-8°C.

In-process controls

Suitable in-process controls are described. Environmental monitoring of operational areas is performed and media fills are performed routinely. Filling machines are cleaned in place/steam sterilised prior to use. Sterile filter integrity is confirmed.

Validation of analytical methods

The validation package described includes details of assessment of sterile filtration, product/filter compatibility, holding times for the bulk solution, and sterilisation/depyrogenation of containers, closures, equipment and components. In addition, environmental monitoring and media fill studies have been described.

Product/filter compatibility has been examined. No degradation or aggregation was observed, phenol content was in order and particulates were within specification limits.

The validation studies confirming the above for somatropin stored in the pressure vessel have been performed. Studies have investigated the protection from microbial contamination. Bioburden samples were all within the acceptance limit. All media fills gave acceptable results.

Validation of sterilisation/depyrogenation of containers, closures, equipment and components has been performed using actual and simulated production conditions including worst case challenges. Acceptance criteria have been defined and satisfactory results of such studies have been provided.

- Control tests on the finished product

The company complies with the requirements of the Ph.Eur. monograph.

Somatropin for injection appears as monograph No. 952 in the European Pharmacopoeia, an updated version of which came into force on 1st January 2000. As Nutropin is a liquid preparation, the test for water cannot be applied to this product. In all other respects however, the monograph is applicable.

Control methods and validation of analytical methods

Full methodologies have been provided for all test methods. A complete justification of the tests employed, together with limits, has been provided. Aggregation, proteolysis, deamidation, oxidation, post-translational modification and lot-to-lot consistency are suitably analysed by the chosen test methods.

Full validation reports have been provided for all methodologies. Use of the various methods for stability testing has also been addressed. The requirements of the Note for Guidance on Validation of Analytical Procedures: Methodology (CPMP/ICH/281/95) are fully met.

The applicant has standardised the potency assay to WHO pituitary-derived (WHO 80/505) and recombinant (WHO 88/624), the current international standards.

Ph.Eur. methods will be used for degree of coloration of liquids, clarity and degree of opalescence of liquids, particulate contamination: sub-visible particles and volume in container (extractable volume).

Batch analysis:
The test results have been generated by Schwarz Pharma, all results were within specification.

- Viral safety

The risk of transmission of viruses is negligible as no primary animal or human sourced materials have been used in the preparation of either drug substance or drug product.

- Animal-derived materials

A number of animal derived raw materials are used in the manufacture of NutropinAq. The origin of the raw material is well documented. Polysorbate 20 is of vegetable origin thereby posing no risk of transmission of TSE.

Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products. The requirements of CPMP/BWP/1230/98 are considered to be fully met.

Stability of the Product

- Formulated bulk

Stability data have been provided for batches of different sizes. The data justify the proposed expiry date of 21 days stored at 2-8°C for formulated bulk drug substance.

- Finished product

Stability reports have been provided for different batches of product. The proposed shelf-life of 18 months at 2-8°C is considered to be acceptable. Storage results for up to 1 month at 25°C justify an in-use shelf-life of 28 days.

Stability studies have been performed using test conditions likely to be experienced under patient use. The product was exposed to normal or intense sunlight during a daily 2 hour excursion from 2-8°C to 25°C for 18 days. The results support the contention that daily short term exposure to ambient temperatures and light does not significantly affect product quality. Repeated or prolonged exposure to direct sunlight is not recommended.

Physical stability of the product has been investigated. Results confirm the robust nature of the product as no changes in visual clarity or monomer content were observed. Somatropin is normally susceptible to surface-induced denaturation and aggregation effects. In conclusion, the results of the study demonstrate that the product should be physically stable over intended product distribution and use.

A clear study protocol for the finished product showing the test conducted and the times when testing is performed has been provided for on-going studies and for the additional batches being added to the programme annually.

Discussion on chemical, pharmaceutical and biological aspects

The applicant relies heavily on experience gained with Protropin and Nutropin, which have been marketed in the USA since 1985 and 1994 respectively. Protropin is a lyophilised product containing somatrem and Nutropin, a lyophilised product containing somatropin. Many of the studies to assess the overall quality of NutropinAq have therefore been carried out by direct comparison with these products.

Satisfactory evidence is provided that product manufacture is well controlled, that consistency of production is achieved and that a stable product results. The requirements of the relevant directives and guidelines are met. The pharmaceutical parts of the SPC, package insert and product label are supported by the information provided in the dossier. A few follow-up measures have been identified, and the company commits to fulfil the requirements after the granting of the Marketing Authorisation.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Pharmacodynamic studies was carried out in order to study the following characteristics:

- Direct and indirect effects of rhGH on growth parameters (body weight gain, growth, bone lengthening)

Studies in hypophysectomised animals

Several studies were performed in hypophysectomised rats. In the vast majority of studies an injection period of 7 days [one day before the onset of hGH-neutralising antibodies] has been applied. The lack of endogenous GH secretion was compensated by the administration of somatrem and somatropin at graduated dose levels alone or combined with IGF-1 or a truncated form of the latter (des-IGF-1). Whereas somatrem and somatropin were given as sc. injections, the IGF-forms were infused by means of implanted osmotic pumps.

Various growth (body weight gain, tibia and femur length, epiphyseal width of tibia, absolute and relative weights of spleen, thymus, liver, heart and kidney) and blood chemistry parameters (serum IGF-1, blood glucose, total protein, urea nitrogen, Ca^{2+}, Mg^{2+}, $^{3-}PO_4$) were measured in order to characterise the effects and efficacy of the administered compounds and combinations thereof.

Somatropin administration led consistently to an almost dose dependent increase of body weight gain, femur and tibia length, spleen and thymus weight and broadening of epiphyseal width. There were no significant differences in the effects of somatrem (rhGH-met) and somatropin (rhGH). The delivery of rhGH by osmotic minipumps produced greater effects than the sc. bolus injection. The combination of rhGH and rhIGF-1 or des-rhIGF-1 yielded greater additive effects than either hormone alone, which was not clearly reflected by serum IGF-1 levels.

The same result was obtained when rhGH (2 mg/kg/day; sc. injection) and rhIGF-1 (2 mg/kg/day sc. infusion by osmotic minipumps) were given alone or in combination for 28 days. Weight gain induced by IGF-1 progressively declined after 4 days, compared with a more maintained effect of rhGH (20). Decrease of serum creatinine and urea nitrogen as well as an increase of phosphate is primarily due to IGF-1 and point to an anabolic status and/or changes in kidney function. However, no clear cut pathological values were obtained.

Studies in genetically fixed hypopituitarism

Two studies were performed in genetically fixed hypopituitaric dwarf rats (dw/dw) treated for seven days.

The effect of the hormones or hormone combinations in the first study was measured by the same parameters as in hypophysectomised rats (see above). In the second study only body weight gain, liver heart, spleen, thymus, kidney weights and serum IGF-1 levels were measured.

As in hypophysectomised animals, a dose dependent increase in body weight gain, tibial length and epiphyseal width was observed in the first study, the combination being more effective than either hormone alone. Organ weight changes (increase of liver, kidney, spleen and thymus weight) are mainly due to rhIGF-1.

For IGF-1 a decrease of serum concentration after rhGH and an increase after the combination were observed. While the increase appears to be a logical consequence of compound administration, the decrease can not be reasonably explained. It can only be speculated that the selected sampling point (24 hours after last administration) does not reflect the true situation representatively.

In the second study the body weight changes were similar in nature to those in the first. rhGH and the combination produced dose dependent increase of spleen weight, the combination having the greater effect. Serum IGF-1 levels increased significantly only after the high rhGH dose.

- Effects on sexual maturation and growth in neonatal and immature (starting at 1 year of age) monkeys

Study in aged rats
Males, approximately 18 months old rats, were treated with 2200 µg/kg/day rhGH by sc. injection or 2400 µg/kg/day rhIGF-1 by sc. infusion (osmotic minipumps) or combinations thereof for 14 days. Similar studies with rhIGF-1, des-rhIGF-1 and recombinant bovine GH (rbGH) were performed for comparative purposes (Rep. 90-151-0320 A,B,C).

In addition to body weight gain and serum chemistry, histology of spleen and thymus, the proliferation and ripening of explanted and cultivated thymocytes and lymphocytes (spleen) were studied in vitro.

As in hypophysectomised and dwarf rats, the hormones produced an increase of body weight gain, rbGH that is less immunogenic in the rat (25) being more potent than rhGH. Larger responses were obtained to combinations than to either hormone alone.

Changes in serum chemistry parameters (decrease of blood urea nitrogen, total protein and increase of phosphate) as well as organ weights (kidney, spleen, and thymus) were generally due to both forms of IGF-1. The same holds true for the increased cellularity of thymus with restoration of thymus architecture and enhancement of in vitro response to mitogens.

Effects on sexual maturation (and growth)
In order to determine whether developmental increase in basal serum LH would occur at an earlier age and menarche and first ovulation would be advanced, groups of 4-6 female rhesus monkeys, 20 months old (approximately 10 months before the expected menarche) were treated with rhGH sc. three times per week for 50 months. To provide a stepwise increase in serum GH levels as occurs during normal development (52; 51) rhGH was administered at a dose of 125 µg/kg from age 20 through 23 months and of 250 µg/kg thereafter.

Body weight, crown rump length, skeletal maturation (scoring hand and wrist radiographs), serum E_2, GH, GH-antibody and LH levels were measured at regular intervals, serum insulin and serum biochemistry (e.g. electrolytes, proteins, glucose, creatinine, cholesterol) at the completion of rhGH treatment (70 months of age). Reproductive performance for each animal per year was assessed.

The mean age at the time of initial rise in serum LH was slightly advanced (26.6±0.4 vs. 31.3±0.3 months) by GH treatment. After this elevation of basal LH secretion, rhGH treatment resulted in a significant increase in serum E_2 levels within 12 hours of injection, which remained elevated through 24 hours. The first ovulation occurred earlier in three of five animals while the other two ovulated at an age similar to that of controls (42±0.4 months). These slight changes do not point to a risk of significant acceleration of sexual maturation, especially LH release.

Long term treatment with rhGH accelerated bone maturation and velocity of increase in crown-rump as well as tibia length and body weight. However, finally only adult crown-rump length was enhanced by about 3% whereas there was only a slight increase in tibia length and body weight. Thus, adult skeletal maturity was reached at an earlier chronological age in treated (68±0.4 months) than in control females (73.4±2.4 months). With regard to serum chemistry, treated animals had significantly lower glucose, creatinine and cholesterol and higher LDH concentrations.

The treatment of 12-14 months old male prepuberal rhesus monkeys (Rep. 91-008-0301-561) with 50 or 350 µg/kg/day rhGH sc. for 6 months resulted in an increase of body weight gain (dose dependently), crown-rump length (high dose), resting insulin (high dose) and IGF-1 levels (both doses).

- Effects on kidney growth and function

In rodents rhGH and rhIGF-1 are able to increase renal mass. Whereas rhGH produces an effect in proportion to body weight, rhIGF-1 increases renal mass unproportionally to body mass. Both peptides increase glomerular and tubular cell proliferation and renal DNA/protein ratio. Even after 60 days of treatment no glomerulosclerosis was to be observed, although extremely high doses were administered. Thus, these results do not point to a particular risk to be expected in children treated with therapeutic dosage.

With regard to renal function, it was shown in studies with isolated perfused kidneys of intact and hypophysectomised rats that rhGH accelerated acid secretion and coupled volume absorption in the range of GH concentrations achieved during episodic GH surges. Furthermore, rhGH administration in vivo to hypophysectomised rats enhanced net acid secretion and urinary acidification, consistent with accelerated tubular H+ secretion as a physiological expression of GH action.

- Effects on liver enzyme induction.

The action and interaction of somatrem (rhGH-met), prednisone and thyroxine on liver enzyme induction were studied in hamsters and rats (University of Utah 1986).

Significant changes were confined to phase I parameters (P_{450}-concentration, p-nitroanisole and ethylmorphine demethylation) which were slightly depressed by somatrem. The somatrem response was not significantly altered by co-administration of thyroxine, prednisolone or both. These changes point to the possibility of mild depression of drug metabolising enzymes under rhGH therapy.

- Summary of salient findings

The mostly dose dependent increase of body weight gain, epiphyseal width, long bone length, spleen and thymus weight in rats confirms the already well known effects of rhGH in rats, with rhGH and rhIGF-1 demonstrating additive effects. No differences in the effects and efficacy of somatrem and somatropin were observed.

Delivery by implanted osmotic pumps resulted in greater effects than bolus injection at equal dose levels. This points to an improvement of efficacy by continuous delivery of small amounts per time unit of rhGH in contrast to bolus administration.

Serum chemistry reflects the anabolic status under rhGH treatment.

Although long term treated animals reached adult skeletal maturity at an earlier chronological age, no disturbance of endocrine regulation significantly affecting growth, fertility, well-being or survival rate could be detected.

The studies on function and morphology of kidneys confirm the physiological expression of GH action.

The possibility of mild depression of P_{450}-dependent drug metabolising enzymes in the liver points to a possible slowing of metabolic drug clearance which has to be considered in case of co-administration of other drugs in therapy. This aspect is already part of therapeutic knowledge.

The documentation of dose dependent increase of body weight gain, epiphyseal width, long bone length, spleen and thymus weight relies mostly on published literature, which is to be considered acceptable.

Pharmacokinetics

- Intact animals

Studies in healthy, normal, adult mice, rats and monkeys indicated that serum clearance was rapid by all species following i.v. administration. Average serum clearance was species-specific and decreased as species size increased. Following i.v. bolus administration, serum concentration versus time curves were bi-exponential. The terminal half-lives increased with species size corresponding to clearance rates.

After sc. administration of somatropin the following results were obtained in healthy, normal, adult rats and monkeys. The data suggest, in addition to species differences in the metabolic clearance rate, further differences in an absorption rate-limited kinetics, whereby the slow absorption from the injection site in monkeys is similar to that in humans.

- Conditioned animals

In bilaterally nephrectomized rats a significantly (3-fold) reduced clearance of somatropin was found following i.v. injection when compared to the results of sham-operated controls. Both initial and terminal half-lives were longer. No effect was seen on the initial or steady-state distribution volume. These results agree with literature reports and suggest that the kidney plays a major role in the systemic clearance of GH.

Hypophysectomy in rats, the most commonly used model for GH efficacy studies, led to reduced clearance (48%) and volumes of distribution (34-37%) following i.v. bolus injection while the half-lives remained unaffected. In hypophysectomised rats the maximum serum concentrations following sc. administration of somatropin were approximately 2-fold higher and occurred later (80 vs. 35 min.) than in control animals. These findings are consistent with the reduced clearance (48%) and volumes of distribution (34-37%) observed following i.v. injection in these conditioned animals.

Tissue distribution and metabolism

Tissue distribution studies were conducted in sham operated and hypophysectomised rats with ^{125}I-somatrem and ^{3}H- or ^{125}I-somatropin. They demonstrated that the liver and kidney are the primary sites of localisation following sc. and i.v. administration and that both compounds have identical distribution profiles. This is in agreement with common knowledge on the distribution and major organs of metabolism of GH in the literature.

The passage across the placenta was studied in rats on the 15th day of pregnancy. Two hours after the administration of 2.5 µCi ^{125}I-hGH the rats were sacrificed, the placentas removed and weighed. The consistent finding of protein-bound radioactivity in placentas and fetuses indicates that rhGH will to some extent pass the placenta in pregnant rats.

Studies with ^{3}H-somatropin provided evidence that rhGH was broken down to ^{3}H-monoamino acids that were reincorporated into newly synthesised plasma proteins.

- Age dependency

The pharmacokinetic profile of somatropin following i.v. administration was compared in adult and juvenile rhesus monkeys to determine the effects of age on rhGH disposition. Statistical comparison of the pharmacokinetic parameters did not reveal significant differences between the two age groups.

- Comparison of somatrem and somatropin and the influence of different formulations

The pharmacokinetic profile of somatrem (rhGH-met) and somatropin (rhGH) following i.v. and sc. administration was compared in male cynomolgus monkeys in a four-period crossover study (Rep. 86-030-0301). Mean serum clearance, initial and terminal half-life, C_{max}, T_{max} and absolute bioavailability were determined.

Statistical comparison of pharmacokinetic parameters for both routes of administration indicated bioequivalence of both products.

In order to examine the possible influence of different somatropin formulations on pharmacokinetics, a series of comparative studies with various research formulations, Nutropin and NutropinAq were performed in rats and monkeys by sc. administration.The somatropin body burden (AUC sc.) produced by the research formulations in rats was substantially (35-49%) lower than that observed after Nutropin administration (Rep. 90-283-0301).

An additional pharmacokinetic study in monkeys comparing Nutropin (lyophilised and reconstituted material) and NutropinAq (liquid material) was performed by sc. administration in a randomised crossover design. The statistical comparison of the pharmacokinetic parameters (AUC, C_{max}, T_{max}) did not reveal significant differences between the two formulations. Thus, the change from a lyophilised, reconstituted to a liquid formulation did not modify the disposition of somatropin in rhesus monkeys.

- Summary of salient findings

The measured pharmacokinetic parameters (mainly C_{max}, T_{max}, $T_{1/2}$, V, AU, Cl) were species specific in mice and rats. Thus, they can only be used for the interpretation of results of pharmacodynamic and toxicity studies in the respective species and does not allow interspecies extrapolations. Even in this restricted consideration particularly those results have to be interpreted with great care which have been obtained with ^{125}I-labelled rhGH.

As ^{125}I-labelled rhGH undergoes in vivo deiodination as well as hydrolytic cleavage of the peptide, neither the total nor the TCA-precipitable radioactivity represents the correct amount of parent compound (30).
Only in monkeys do some parameters appear to be similar to those in humans, although, in contrast to humans, no specific GH binding protein could be identified.

With regard to the administration of NutropinAq to humans it can be concluded from the pre-clinical pharmacokinetic data that no significant differences should be expected:
- in somatropin kinetics following Protropin, Nutropin or NutropinAq,
- in different age groups of patients

Mice, rats, guinea pigs, rabbits, cynomolgus and rhesus monkeys were mostly used for the testing of NutropinAq. With the exception of guinea pigs, in which specific GH-binding proteins (GHBP's) in serum were undetectable, all other species and humans were found to have specific serum GHBP's, however of different specificity and affinity.

The actions of GH in tissues and organ systems are mediated by specifically binding proteins, the receptors, which are heterogeneous in structure and intracellular distribution in the various species.Specifically binding proteins in plasma and receptors are both part of an integrated biological system. Therefore, from the observed species differences it has to be concluded that quantitative extrapolation from animal experiments to humans is not possible with regard to pharmacodynamics, pharmacokinetics and toxicodynamics of NutropinAq. Only qualitative extrapolations with regard to the effect-profiles are justified.

It is supported that interspecies extrapolation of effects generally constitutes a complex issue. Nevertheless, valid in-vitro or animal models have been established and are indispensible for research. This applies also to the biological effects of growth hormones.

Toxicology

- **Single dose toxicity:**

No studies were conducted. The source of this information about acute toxicity is invalid regarding information about the purity of the substances and relies on several sources of documentation.

- **Repeat dose toxicity:**

A survey on repeated dose toxicity studies by sc. administration has been submitted. Complete hematology, serum chemistry, gross and histopathological evaluations were performed in most of these studies. The formation of antibodies to rhGH was monitored in the 2-week rat and 2-, 13-week and 12-month monkey studies.

Rats

Rats injected subcutaneously with up to 3125 µg/kg/day of somatropin for 14 days did not exhibit any significant signs of toxicity. The mean body weight of the high-dose females was higher than that of the concurrent controls.

Hematology and serum chemistry parameters were unremarkable. Antibodies to rhGH were detected in rat serum samples at study termination. However, no histological evidence of immune complex formation was observed.

At terminal necropsy, male rats in the 625 and 3125 µg/kg/day groups had elevated adrenal weights that correlated with microscopic evidence of minimal hypertrophy of the adrenocortical cells in most animals. The dose of 125 µg/kg had no effect. The treatment responses noted in this study were considered to be the reflection of an exaggerated pharmacodynamic effect and/or of no toxicological significance.

In the 2-week study positive antibody titers were noted in at least 50% of the monkeys from all dose groups by the end of the observation period, with the exception of one high-dose animal in the 13-week study (transient low titers) no other animals were affected. Serum concentration of the test article was determined in samples collected four hours after the final injection indicated an essentially dose-dependent increase in systemic absorption.

While the animals in the 2-week study were not sacrificed, no treatment-related gross or microscopic lesions were observed in the 13-week study.

Monkeys

Two separate toxicity studies were conducted in rhesus monkeys, in which somatropin was administered 3 times a week at doses from 125 to 625 µg/kg for 2 to 13 weeks. Following completion of dosing in the 2-week study, animals were observed for an additional eight weeks for the assessment of potential antibody responses to rhGH. The dosing regimen was well tolerated in both studies. There was no evidence of overt toxicity and no significant changes in hematology or serum chemistry parameters were observed.

The sc. treatment of cynomolgus monkeys (about 24 kg body weight) over 52 weeks was tolerated without compound-related mortality and did not reveal any significant compound-related alterations with regard to clinical observations, laboratory investigations, organ weights, gross and microscopic post-mortem examinations. Also at the injection site nothing other than needle traumas could be identified. No evidence of antibody formation was found (33).

In the 50-month treatment study in monkeys which was initiated at 20 months of age, somatropin accelerated bone maturation, growth velocity of crown-rump and tibia length and body weight. The period of acceleration occurred coincidentally with the occurrence of spontaneous puberty. The final adult crown rump length was increased by about 3%. One animal exhibited higher estimates of antibodies to rhGH throughout the study period and also had a smaller increment in crown-rump length. No other deviations or adverse effects were observed.

- **Genotoxicity:**

Reports or publications on the testing of rhGH in well established genotoxicity study models were not available. However a survey of the data available has been presented.

Mice

The treatment of Snell dwarf mice with cadaver-derived and recombinant hGH (rhGH-met) at dosages of 150 mU/animal/day sc. (= about 2.5 mg/kg/day based on assumptions: 3 IU = 1 mg; 20 g body weight) for 4 weeks produced significantly increased frequencies of chromosomal aberrations in bone marrow cells as measured by the micronucleus test. The effect is obviously dose dependent.

In vitro studies

In vitro treatment of CHO cells with the two types of hormones; cadaver-derived and recombinant hGH (rhGH-met) (36 or 360 mU/ml = 12 or 120 µg/ml) likewise induced structural chromosomal aberrations.

The monitoring of chromosomal abnormalities in peripheral blood lymphocytes in twelve idiopathic GHD patients over 12 months of GH therapy did not reveal an increase when compared with age-matched healthy control.

This finding is not necessarily in contrast to studies on chromosome fragility in lymphocytes of GH treated children (Tedeschi et al. 1993), in which an increased fragility induced by bleomycin in vitro was found after 6 months of GH treatment, as the meaning of this finding for safety assessment remains debatable.

The CPMP/ICH/302/95: Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals states that the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. This is relevant for rhGH, which however is a growth promoter, giving rise to promoter effect in studies in combination with bleomycin. The lack of traditional genotoxicity studies is justified and the promoter effect indicating increased cancer risk upon long term treatment should be taken into consideration in indications for long term use of rhGH therapy.

- **Carcinogenicity:**

No regular tumorigenicity studies fulfilling current requirements with regard to starting age of animals, group size and duration of treatment were performed either in rodents or in any other species. However a survey of the data available has been presented.

In order to study the influence of rhGH on virus induced leukaemia, a high leukaemic retrovirus-infected mouse strain (AKR/O-mice) was treated sc. with 200 µg/kg/day (day 5-50 or 40-140). The authors came to the conclusion that rhGH did not influence the development of malignancy in this model.

No tumorigenic potential with regard to tumour initiation for humans can be derived from knowledge gained in preclinical studies. However, as anabolic and mitogenic effects in vitro and in vivo at supraphysiological concentrations or dose levels respectively have been described, a promotional effect on tumour growth in tumour bearing patients might be considered.

No new regular carcinogenicity studies were performed. The promoter effects of GH are demonstrated and suspected from the biological nature of GH and have been be included in the SmPC.

- **Reproduction Toxicity:**

No common reproduction studies (studies on fertility, embryotoxicity, pre- and postnatal toxicity) were conducted. However a survey of the data available has been presented.

Rats
Female rats were treated with rhGH at dose levels of 0.3, 1.0 and 3.3 IU/kg (=300; 1 000; 3 300 µg/kg) daily for two weeks before mating, throughout mating and during the first seven days of pregnancy. The two higher dose levels produced a significant prolongation of the estrous cycle. The prolongation (studied after highest dose) appears to be associated with increased plasma progesterone levels. The number of early resorptions was increased after the highest dose level and the number of viable offspring after normal delivery after the mid dose. Fetal body weights were increased at all rhGH dosages

Studies in rats, in which daily sc. injections of natural GH during pregnancy of rats (total dose 1.4-2 mg/animal = about 8 mg/kg) yielded no other effects in the offspring than a significant increase of the mean birth weight.

Monkeys
Somatropin (250 µg/kg) was given sc. three times weekly to immature female rhesus monkeys (n=5) to determine whether developmental increases in basal serum LH would occur at an earlier age and if menarche and first ovulation also would be advanced. The females where studied from 20 months of age until occurrence of first ovulation.

The mean age at the time of the initial rise in serum LH was advanced by rhGH treatment (29.6 $\pm$ 0.4 versus 31.3 $\pm$ 0.3 months) as was the time of first ovulation (31.5 $\pm$ 0.7 versus 43.5 $\pm$ 0.3 months).

However, these changes obviously did not disturb the general reproductive performance. The same treatment was continued over 50 months (4.2 years). Reproductive performance for each animal for each reproductive year was assessed on the number of confirmed pregnancies (based on twice weekly progesterone analyses), spontaneous abortions or stillbirths, or live births with infants living for at least a month. All females had at least 3 successful pregnancies. The proportion of years in which they had a live birth was not different from control animals (0.73 $\pm$ 0.08 versus 0.79 $\pm$ 0.07).

No increased risks of disturbances of fertility, delivery, nursing and development of the pregnancy can be derived from these animal experiments. The experiments are however sparse.

Dogs
Male dogs were exposed to 3, 10 or 25 IU/kg/day (= 1, 3.3 or 8.3 µg/kg/day) of pituitary derived hGH or rhGH-met given sc. for 20-28 days. The highest dose caused marked reduction of plasma prolactin, LH and testosterone levels associated with reduction of testes and prostate weights, degeneration of germ cells and epithelial atrophy in testes, degenerative changes in epididymis and reduced height of the prostatic epithelium. Similar, although less severe morphological changes were observed after the medium dose.

The results indicate that repeated administration of very high doses of hGH interferes with the hormonal regulation of the testis in the dog.

Thus, the possible interference of rhGH administration at high dose levels to male human beings with pituitary function, especially gonadotropin secretion needs to be considered.

Experimental animal studies, although only of limited value for the safety assessment of rhGH for humans, did not indicate that this hormone could lead to disturbances of male and female fertility, pregnancy, delivery, nursing and development of the progeny when administered at therapeutic dosages.

It is supported that no further reproductive toxicity testing within a regulatory context is justified. Moreover, no explicit warning about inadvertent consequences of accidental somatropin administration during pregnancy is necessary and no related warning is actually incorporated within the SPC or PL.

It is argued, however, that the role of GH in (early) human pregnancy is far from being sufficiently understood and that the single reported case of GH substitution during early pregnancy (Müller et al. 1995) is largely insufficient to justify more broadly the GH substitution in GH-deficient pregnant women. The company apparently follows this argumentation since a precautionary statement has been included in the SPC that NutropinAq should be discontinued if pregnancy occurs. This should apply until valid and formal clinical data are available which document the favourable risk-benefit ratio of GH substitution during early pregnancy in GH-deficient women.

- **Local Tolerance:**

Rabbits

In order to assess the safety of somatropin at the application site, local tolerance studies were performed in rabbits by single administration.

Sc. and **i.m.** administration of somatropin to rabbits was well tolerated locally. Gross and microscopic findings were limited to those related to the mechanical trauma of injection and unrelated to the formulation components. This holds particularly true for those formulations containing phenol (2.5 mg/ml) and polysorbate 20 (2 mg/ml) (Rep. 93-005-0301) and is in good agreement with the results of clinical studies with NutropinAq in which even after 3 years of sc. treatment no increase of allergies and local adverse reactions was observed (see Clinical Documentation).

Additionally, prior to sacrifice (1, 3 or 7 days after sc. dosing), three rabbits/group received a single i.v**.** injection at a dose volume of 0.5 ml (2.5 mg/animal) of the test or control formulation into a marginal ear vein to evaluate pain response (Rep. 91-025-0301). All of the formulations were well tolerated locally, no significant lesions were evident at the sites of injection and test material-related responses to pain were not apparent.

This is in good agreement with the results of repeated dose studies (see above) in which even after sc. daily long-term administration over 52 weeks no local adverse effects other than needle traumas were diagnosed.

Thus, no substantial adverse local reactions at the application site should be expected in humans. This reasoning is acceptable in light of the extensive human experience.

- **Other toxicity**

Antibody formation:

Routine sensitisation studies in guinea pigs were not performed. However a survey of the data available has been presented.

The monitoring of antibody formation in the 2-week rat study (daily administration) revealed rhGH-antibodies at termination. However, neither clinically nor histopathologically could signs of antigen-antibody reactions be observed.

After daily sc. administration of rhGH and rhIGF-1 (2 mg/kg/day) to rats antibodies against rhGH were present at day 26, with titre being negatively related to weight gain, serum IGF-1 and acid labile subunit binding protein.

In the 2-week study in monkeys positive antibody titers were noted in a dose dependently increasing incidence (33; 50; 83%) and in a total of about 50% of all dosed animals by the end of the 8-week post-treatment observation period. Only one high dose (625 µg/kg) animal of the 13-week study showed transient (week 6-10) low antibody titers.

Moreover, no antibodies to somatropin were found in rhesus monkeys treated daily with 350 µg/kg sc. over half a year or in cynomolgus monkeys which received daily sc. administration of 60-600 µg/kg for 1 year.

The antigenicity of somatropin for human beings is considered to be very low.

Of particular value for the prediction of the immunogenic potential of rhGH in human beings appears to be a transgenic-mouse-model (43; 44).Transgenic mice express hGH ectopically, predominantly in the salivary gland, thus representing an animal model producing hGH as a „self-protein". This transgenic mouse model of antibody formation was used as a tool for screening of rhGH preparations for immunogenic potential. A pool of three samples of thermally stressed NutropinAq to produce a degradation profile the same or worse than that predicted for a sample stored at 28°C was used. Following 12 weeks of twice weekly sc. injections no detectable antibodies were found.

Thus the conclusion that 18 month storage at 2-8 C, has a low antibody forming potential, is considered to be acceptable.

Impurities, aggregation and degradation products:
Aggregates and clipped forms of somatropin do not constitute a relative part of NutropinAq.
Oxidised and deamidated somatropin can form a relatively large part (up to 23 %) of the somatropin content of aged or thermally stressed NutropinAq. Oxidised and deamidated somatropin retained full GH bioactivity and the potential to induce adverse reactions or antibodies in humans was considered identical to native somatropin.

An evaluation of the excipients polysorbate and phenol used in NutropinAq, was presented and did not reveal any health risk.

- **Ecotoxicity/Environmental Risk Assessment:**

Somatropin is identical with the naturally occurring human growth hormone. This peptide hormone is rapidly and completely degraded by enzymatic hydrolysis in the human organism. Thus, the therapeutically administered compound is not released into the environment.

Inadvertent release of wasted material would also not cause any problems in the environment due to its peptide structure which will be rapidly destroyed and mineralised by microbial hydrolytic processes. Therefore, no environmental risk can be expected from the introduction of NutropinAq into therapy.

Discussion on toxico-pharmacological aspects

The pharmaco-toxicological dossier was considered an adequate documentation for NutropinAq. No major preclinical objections existed against granting a marketing authorisation for NutropinAq and the points for clarification were resolved satisfactorily.

In vitro and in vivo preclinical and clinical testing have demonstrated that NutropinAq is therapeutically equivalent to pituitary derived human GH (hGH). Treatment of paediatric patients who lack adequate endogenous GH secretion, patients with chronic renal insufficiency and patients with Turner syndrome results in increased growth rate and an increase in insulin-like growth factor I (IGF-I) levels.

Effects on pituitary functions were seen in reproductive testing and promoter effects were found in genotoxicity and tumorgenicity studies. These observations indicating increased cancer risk upon long term treatment should be taken into consideration in indications for use of rhGH therapy.

The response to the CPMP Consolidated List of Questions satisfactorily answered the raised issues regarding protein binding of rhGH in animals, the lack of reproductive toxicity studies, as well as the evaluation of impurities, excipients, aggregation and degradation products.

No local reactions and immunogenicity is expected in humans, due to the identity of rhGH with somatropin.

Three single dose kinetic studies, three repeated dose toxicity studies (2-week rat; 2 and 13-week monkey) and two local tolerance studies have been conducted according to GLP. The other study reports and published papers originated from universities or were from dates before GLP-requirements. References cited in the expert report follow the list of references provided by the applicant.

No environmental risk is expected from the introduction of NutropinAq into therapy and no studies were conducted.

The recommendations for SPC modification given from the pharmaco-toxicological perspective have been implemented.

In conclusion, the pharmacological-toxicological assessment is in favour of granting a marketing authorisation for NutropinAq.

4. Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

No pure pharmacodynamic studies have been performed in humans with Nutropin or NutropinAq.

Protocol 85-031. Study of Nutropin short-term in normal adult males

Initial examinations of Nutropin was carried out in 10 healthy young adults. Subjects received four days of treatment with 0.125 mg/kg/day given as subcutaneous injection. There were no clinically important changes in vital signs. However, eight of the ten subjects reported subjective symptoms reflecting fluid retention. Body weight of subjects had returned to baseline four days after last dosage.

Serum GH concentration peaked after 4-5 hours, but returned to baseline before next injection. However, a marked increase in somatomedin-C (now better known as Insulin-like Growth Hormone I (IGF-1)) was observed, which peaked on the last day of evaluation. Thus, it was not possible to conclude at what concentration this pharmacodynamic action would reach plateau. Plasma concentrations of IGF-1 were determined by a radioimmunoassay validated at Genentech. The intra-assay and inter-assay variations of the assay were < 20% with largest variations at low concentrations. Plasma samples were taken with EDTA, and heparin was avoided to exclude possible interference from IGF-1 binding proteins.

Metabolic changes included as expected an increase in fasting blood glucose and in blood glucose following glucose challenge. The changes were, however, small.

Pharmacokinetics

(see ICH/CPMP Note for guidance: E5, interaction, bio-equivalence)

No pharmacokinetic studies have been performed with patients in the proposed categories of indications, where patients with growth hormone deficiency due to their altered metabolism and body composition might have a different absorption following s.c. injection as well as an altered half-life elimination. Pharmacokinetics were also not studied in children or elderly or patients with renal or hepatic impairment.

The pharmacokinetics of Nutropin was studied in healthy male volunteers in 5 studies involving a total of 119 subjects. No multiple dose pharmacokinetic studies were performed

- General:

Absorption

A pharmacokinetic study (M0019g) was performed in 21 healthy young adults as a cross-over study with single dose Nutropin 0.1 mg/kg administered s.c. or single dose Nutropin 0.02 mg/kg administered i.v. with a seven-day washout period. Following the s.c administration of, Nutropin was absorbed slowly with Tmax of 6.0 ± 0.37 hr and a Cmax of 75.2 ng/ml.

The fraction absorbed after s.c. injection (bioavailability) was 81 ± 5 % (study M0019g)

Distribution
Following i.v. administration of 0.02 mg/kg (study (M0019g) the initial volume of distribution was 30±10 ml/kg. The steady state volume of distribution was 51±8 ml/kg.

Metabolism
The metabolism was not studied

Excretion
Following i.v. administration (study M0019g) of 0.02 mg/kg, the half-life was 22 min. The half-life following s.c administration was considerably longer (2.5 hr) indicating absorption-rate limited pharmacokinetics after s.c. injection.

- Interaction studies:

No interaction studies were performed.

- Bioequivalence studies:

Initial pharmacological assessment of Nutropin (somatropin) was performed with the formulation G042A. In the further development of Nutropin a new formulation (G072A) was produced. A bioequivalence study was performed in 24 healthy young adults as a cross-over randomised study of Nutropin formulations G042A and G072A following single dose 0.1 mg/kg as subcutaneous injection. Each subject was examined with at least a six-day washout period between injections. Serum concentrations were assessed with the assay previously described.

The two formulations were considered bioequivalent based on standard criteria. The ratios of the means for the AUC parameter have 90% confidence intervals well within the 20% criterion for bioequivalence

A bioequivalence study was performed in 38 healthy young adults as a cross-over randomised study of Nutropin formulations G114AB (Liquid) and G072A (lyophilized) following single dose 0.1 mg/kg as subcutaneous injection. Each subject was examined with at least a six-day washout period between injections.

The two formulations of Nutropin were considered bioequivalent since the ratio of geometric means of AUC and 90% confidence intervals are well within the 20% criterion for bioequivalence.

A confirmation of the study above was performed with another product code of Nutropin Liquid (product code G108AB), but with identical design. In 36 healthy young adults a cross-over randomised study of Nutropin formulations G108AB (Liquid) and G072A (lyophilized) following single dose 0.1 mg/kg subcutaneous injection was performed. Each subject was randomised to one of the two treatment sequence groups with a seven-day washout period between injections. Serum concentrations were assessed with the assay previously described.

The two formulations of Nutropin are bioequivalent since the ratio of geometric means of AUC and 90% confidence intervals are well within the 20% criterion for bioequivalence.

All individual bioequivalence studies documented have demonstrated equivalence satisfactorily. It is noted that bioequivalence between the very first lyophilised formulation (G042A) used in the clinical development program and the marketed NutropinAq has not been investigated directly. However, based on indirect comparison of the bioavailabilities, the NutropinAq and G042A formulations can be considered bioequivalent.

- Summary of salient findings

The pharmacokinetic data are not complete. However, the available data on the pharmacokinetics of Nutropin are in agreement with published reports on other recombinant human growth hormone products. Considering the fact that growth hormones have been used extensively in the proposed target population, the pharmacokinetic documentation is considered acceptable.

Clinical efficacy

Main studies

The clinical efficacy and safety of Nutropin have been evaluated in each of the four indications, where somatropin therapy has evolved as part of clinical practice over the last decade. All four indications are approved for other brands of recombinant human growth hormone.

- Growth Hormone Deficiency (GHD) in Childhood

No placebo-controlled studies have been performed.

Protocol 86-061

For patients completing 12 months treatment with Nutropin in studies 85-041 (previously untreated patients) or 85-042 (previously treated patients) an extension of open-labelled Nutropin treatment were performed with the intention to follow up until adult height had been reached. Treatment was discontinued when the growth rate declined to < 2 cm/year or when the bone age had reached > 15 years (boys) or >14 years (girls). Ninety-two patients were enrolled in 21 centres in the USA. The dosage was 0.3 mg/kg/week given subcutaneously three times per week. For patients with suboptimal growth response (defined as < 8 cm/year) it was decided to gradually (every 6 months) increase Nutropin dose by 0.15 mg/kg/week up to a maximum of 0.6 mg/kg/week. The dose was adjusted for weight annually. After the second year of study patients were randomised to receive the weekly dosage either as three injections per week or daily injections. After the third year of study all patients were assigned to receive daily injections. Patients were initially treated with Nutropin formulation G042A; Nutropin formulation G072A was phased into the study. Previous bioequivalence assessments had confirmed the equivalence between the two formulation codes.

Efficacy results from study 86-061 have been submitted as height SDS data. For patients with childhood GHD, it is confirmed that prolonged therapy with NutropinAq (60 months, n=60) is followed by improvement in height SDS. Baseline values for patients were –3.4 ± 1.3, which improved to –0.9 ± 1.4 after 5 years of therapy.

Protocol 87-070; *Daily injections in naive and previously treated patients.*

An open-labelled, uncontrolled study of Nutropin was performed to assess the efficacy and safety of Nutropin administered as daily subcutaneous injections to children with GHD. Patients were enrolled in two cohorts. Cohort 1 (n=63) included patients not previously treated, whereas cohort 2 (n=9) had received prior treatment with either pituitary-derived GH or Protropin for varying periods of time. All children were prepubertal and bone age was < 10 years for girls and < 11 years for boys (for baseline characteristics, see table 7). GHD was documented by a maximum GH response of < 10 ng/ml on two standard tests of GH secretory capacity together with a growth rate < 5 cm/year. The dosage was 0.3 mg/kg/week given as daily injections (0.043 mg/kg/day). The dose was adjusted for change in weight annually. Treatment was discontinued at a growth rate < 2 cm/year or when the bone age had advanced to > 15 years (boys) or > 14 years (girls).

Efficacy was confirmed with a significant improvement in growth rate on initiation of Nutropin therapy. On continued treatment the growth improvement waned as has been seen with other brands of human GH. Nevertheless, up to 4 years of therapy annual growth rate remained higher than at baseline (table 8). To what degree the emergence of pubertal spurt influences this is not discussed in the report.

Efficacy results from study 87-070 have been supplied as height SDS data. For patients with childhood GHD, it is confirmed that prolonged therapy with NutropinAq (48 months, n=47) is followed by improvement in height SDS. Baseline values for patients were –3.0 ± 1.3, which improved to –0.8 ± 1.2 after 4 years of therapy.

Phase III study L0368g: *Untreated patients with GHD treated with Nutropin Liquid.*
The primary objective of this study was to demonstrate the safety of NutropinAq, secondary objectives were to measure growth rate and change in height standardized for age and sex as well as height age and bone age.

This is a multi-centre (17 North American pediatricians) open-label, non-randomised, single arm safety and efficacy study of Aq. No control groups were used.

A total of 67 (planned 60) children with previously untreated GHD were enrolled and treated with 0.043 mg/kg of body weight of NutropinAq, given by daily s.c. injections. Adjustments in the dose were made at 6-month intervals.

Inclusion criteria for naive or previously treated children with growtrh failure were the following:
GH deficiency was to be documented by a maximum GH response of less than 10 ng/ml in two standard pharmacological tests of GH secretory capacity; prepubertal, bone age of 10 years or less for girls and 11 years or less for boys; children with other hormone deficiencies were to be stabilised on levothyroxin or/and hydrocortison prior to enrolment.

Baseline data for patients in study L0368g have been submitted recently. Mean height SDS was –2.7 for this group of 67 children. The inclusion of subject 49807 AYV with baseline height SDS + 0.6 probably relates to a delayed bone age and a low prestudy growth rate. All other children had height SDS below zero at baseline.

Appropriate historical control comparisons were made with results from Study 87-070 (lyophilised Nutropin) with respect to the incidence of antibodies to GH, laboratory safety data, adverse events. The paired t-test is used to evaluate the change in growth rate and in standardised height. The t-test was also used to compare the change in bone age with the change in height age.

The mean growth rate increased from 4.7 cm/year to 12cm /year after 6 months of treatment and to 11 cm/year after one year. For patients followed for a longer period the growth rate was 8.8 cm in the second year. Height SDS increased from a mean of -2.7 before treatment to - 1.6 and -1.1 after one and two years of treatment, resp. The improvements in growth were not accompanied by undue advancement of bone age. There was a highly significant rise in IGF-I plasma levels at therapy. Mean IGF-I score increased from —2.6 at baseline to 0.0 at month 12.

The final reports of studies 85-041, 87-070 and L0368g have recently been submitted. Included are data on near final height for the children followed in these studies. In children with GHD, delayed puberty and late epiphysial fusion is common. A conservative estimate is produced for the end-point final height, since last measurement is generally obtained at bone age >= 14 years for girls and >= 16 years for boys. A further growth into final adult height is still possible after this point in time although typically by only a few centimeters. A combined calculation for 30 boys in the three studies give final height 171.7 cm with height SDS –0.7, which reflects satisfactorily growth improvement. For girls, the same figures are 154.5 cm final height with height SDS – 1.2. These end-points compare favorably with results obtained for the same indication with other brands of rhGH.

- Growth Retardation in Children with Chronic Renal Insufficiency (CRI)

Protocol 87-069; *Children with chronic renal insufficiency.*
A randomised, double-blind, placebo-controlled trial was performed in prepubertal children with chronic renal insufficiency (GFR < 75 mL/min/1.73 m2) with growth retardation despite optimal conservative management. The study period was 2 year, and after this open Nutropin treatment was offered to all patients. The study is strengthened by the long double-blind, placebo-controlled period. 125 children were enrolled; 43 placebo and 82 Nutropin.

Nutropin dosage was 0.05 mg/kg/day s.c. A special condition in the trial was a temporary discontinuation of Nutropin if the child reached his/her mid-parental Tanner target height percentile. In such cases Nutropin therapy was later reinstated without further pause if the child had a growth rate < 3.5 cm/year.

Changes in height SDS values during the 2-year double-blind period documented a marked improvement in growth on Nutropin therapy in contrast to no improvement in children on placebo. The differences are statistically highly significant.

On continued treatment further improvement was obtained although the number of patients is smaller. On initiation of Nutropin patients in the placebo group demonstrated a catch-up growth comparable to the Nutropin group.

Protocol M0079g. *Children with chronic renal insufficiency*
A randomised, double-blind, placebo-controlled trial similar to study 87-069 was performed in 70 patients (for baseline characteristics, see table 22). Patients were prepubertal children with chronic renal insufficiency (GFR < 40 mL/min/m2) with growth retardation (< fifth percentile for chronological age) despite conservative management. The study period was planed as 2 years double-blind, placebo-controlled after which open Nutropin treatment could be offered to all participants.

During the first year of treatment with Nutropin the mean increase in bone age was 1.0 year, so no undue advancement of bone maturation was observed. The calculations for predicted adult height consequently showed improvement after 1 year therapy.

Long-term data for studies 87-069 and M0617n have now submitted. For 33 children followed for 60 months a growth improvement is maintained on prolonged Nutropin therapy. Height SDS at baseline of –2.8 ± 0.8 changed to-1.1 ± 1.0 after 3 years and –0.9 ± 1.2 after 5 years of therapy. The final study reports for studies 87-069 and MM0079g are supplied. After approval by the FDA in 1993 for the indication chronic renal insufficiency in children the remaining patients in the two studies were enrolled in phase IV studies M0617n and M0618n to continue monitoring.

Combined data for 41 patients followed for 60 months on Nutropin confirms continued growth improvement for each 12 months interval. Baseline height SDS of –2.9 ± 0.9 improved to –1.9 ± 1.0 after 1 year, to –1.1 ± 1.1 after 4 years and for –0.9 ± 1.2 after 5 years.
It is acknowledged that for the group of children with CRI several factors make it very difficult to follow until final adult height. This has also been the experience with other products of rhGH. The long-term data provided, confirms the positive impact on growth rates in this indication. From the literature is reported that following renal transplantation the height SDS is maintained and catch-down is not occuring.

Regarding the dosage used in clinical trials of CRI children, it is acknowledged that in the field of GH therapy in CRI no classical dose-response pharmacology has been established, and international experience has generated a ”standard” dosage for this indication as reflected in the SPC for somatropin products.

- Growth Retardation in Children with Turners Syndrome

Protocol 85-044. Two dosage schedule in Turner syndrome
A randomised trial was performed in girls with Turner syndrome and growth retardation to compare two dosage schedules of Nutropin with a cumulative weekly dose of 0.375 mg/kg subcutaneously. A total of 117 patients were enrolled and randomised to no treatment (n=9), Nutropin three times weekly (n=36) or Nutropin daily (n=72). The primary study period was 1 year.

The study design is complex since later amendments included initiation of daily Nutropin to patients in the untreated control group after 1 year, and to treat all patients on a daily schedule (0.054 mg/kg/day), and to randomise patients to early versus late addition of estrogen therapy, and finally to follow the patients until adult height is achieved.

A total of 63 patients are available for assessment of efficacy in the trial. Historical controls were included in the assessments since no group in the trial continued beyond 1 year without active treatment. Since final adult height was the primary end-point is was necessary to include historical controls.

The short-term results observed demonstrated an improvement in growth rate in patients treated with Nutropin. The mean growth rate for 1 year was 6.7 cm in the three time weekly group and 8.1 cm in the daily group. The difference between the two Nutropin schedules is statistically significant ($P < 0.0001$). Both growth rates were significantly greater than in the control group (4.0 cm), $P < 0.0001$.

Due to the complexity of the protocol long-term efficacy is expressed for different groups of patients depending on Nutropin and estrogen treatments given in relation to the age of the patient at inclusion. The results obtained are compared with historical controls for reasons described above.

The growth improvement is demonstrated in all groups receiving Nutropin with the most pronounced increases in patients treated early with Nutropin and later with estrogen. Furthermore, from individual data presentations it is shown that a considerable numbers of Turner girls have changed position on the growth curves approaching normal controls

The differences in final height related to start of estrogen therapy is mainly explained by the influence on bone maturation with fusion of epiphysis at a younger age if estrogen is started early in adolescence.

- Growth Hormone Deficiency (GHD) in Adults

Protocol M0431g: *Growth Hormone Deficiency (GHD) in Adults*
A pivotal trial was performed in 171 patients with GHD acquired in adulthood (age > 18 years). The design was randomised, double blind and placebo-controlled for 1 year. Subjects received daily injections of either Nutropin or placebo. The dosage of Nutropin was 0.0125 mg/kg/day for the first month. A later amendment described a dose reduction to 0.00625 mg/kg/day if side effects reflecting fluid retention occurred. However, 79% of subjects remained on a dosage of 0.0125 mg/kg/day throughout the 12-month treatment period. The initial design of dose intensification after the first month was cancelled. The primary end-points for efficacy were 1) changes in body composition of percentage body fat and lean body mass, 2) strength and endurance during dynamometry, and 3) quality of life.

A total of 171 patients were enrolled in the study. Patients had acquired GHD during adulthood as a result of hypothalamic-pituitary disease. Deficient GH secretion (< 5 ng/ml) was confirmed by two stimulation tests. No patients had a previous history of GH therapy, but they received hormonal treatment as appropriate for other endocrine systems. Patients with malignant diseases were excluded. A total of 125 patients were assessable for the primary efficacy analysis.

Subjects receiving Nutropin had no significant change in mean body weight, i.e. the unfavourable increase in BMI was not influenced. After 1 year of therapy, however, changes in the composition of the body were observed. Total body percent fat decreased whereas total body percent lean mass increased. Nutropin therapy is associated with fluid retention, which could influence the assessment of lean body mass.

Besides these small, although statistically significant, changes in body composition no improvements were obtained in strength and endurance or quality of life. The potential for further improvements during long-term therapy beyond 1 year is not known from this study.

Likewise, it is unknown if a waning efficacy on prolonged therapy, described for other indications, emerges. Bone mineral density (BMD) as assessed by DEXA showed no statistically significant changes.

Protocol M0381g: *Previously treated adults with GHD*
This trial enrolled young adults (ages 18-35 years old) with documented GHD acquired in childhood. The study was randomised, placebo-controlled for two years. The patients had received GH therapy in the past (mean 14 years), but not for at least 1 year prior to study screening. Patients were randomised to daily subcutaneous injections of Nutropin 0.0125 mg/kg (n=20), Nutropin 0.025 mg/kg (n=23) or a similar volume of placebo (n=21). During the initial 3 months of therapy patients received one-half the indicated dose (to reduce side effects of fluid retention). After 3 months patients had to receive the original dose or to discontinue from the study. Concomitant therapy for other hormonal deficiencies was given as appropriate. Efficacy end-points were changes in percent lean body mass and total body fat, strength and endurance, bone mineral density (BMD), and quality of life.

Primary efficacy results showed a statistically significant decrease in percent body fat with a parallel increase in lean body mass. The changes were similar in the two dose groups of Nutropin, whereas placebo did not influence these end-points.

Kinetics of the measurements showed the change in percent fat to occur during the initial 6 months of therapy (of which the first 3 months prescribed one-half dosage) with no further alterations at month 12. It is unclear if efficacy measurements remain unchanged beyond 1 year.

Physical performance as expressed by maximum rate of oxygen consumption increased slightly in the Nutropin groups after 12 months of treatment, but no statistically significant difference from the placebo group was found. Assessment of quality of life did not improve from baseline to month 12 evaluation in either of the Nutropin groups. Bone mineral density in spine did not change at any group at month 6, whereas in Nutropin 0.025 mg/kg/day a small increase was observed at month 12 ($P = 0.03$ compared with placebo). Nevertheless, there were no statistically significant between-group differences in percent change in spine BMD from baseline to month 12. Quality of life and echocardiography were not influenced by NutropinAq therapy.

At the completion of the 24-month treatment significant increase in spine BMD was found in the Nutropin groups, whereas patients treated with placebo as expected showed no difference.

Lipid metabolism shows abnormalities in adults with GHD. Results for the initial 1-year treatment period reveal only small and unclear changes in lipid variables. Total cholesterol and LDL cholesterol were reduced in the high dose Nutropin group, whereas triglycerides remained unchanged. However, the standard variations were often large and low dose Nutropin had no effect at all and even tended to increase triglycerides and cholesterol levels.

Clinical safety

- *Overall Summary of Safety for the indication GHD in children*

Exposure
Number of patients exposed to treatment as well as mean duration of exposure and number of patients years of exposure is listed in table.

Study	No of patients exposed	Mean duration of exposure (years)	No of patient years of exposure (years)
87-070	72	4.6	328
86-061	92	5.1	494
L0386g	67	1.2	80
Total	231	-	902

Adverse events
No overall resume of adverse events was presented. The vast majority of the adverse events were considered unlikely to be related to Nutropin treatment. In study 86-061 none of the non-serious adverse events were considered to be related to Nutropin treatment. In studies L0386g and 87-070, 15 patients reported at least one AE which was considered possibly/probably related to treatment (table 16). The difference in frequency of possibly/probably related AE's between the two studies is explained by more complete and comprehensive reporting of AE's during the more recent L0386g study.

Serious Adverse events
9 SAE's were reported. Out of these only 2 were considered to be related to Nutropin treatment (two cases of recurrence of intra-cranial medulloblastoma).

Withdrawals due to AE
A total of 12 patients were withdrawn from study medication due to adverse events (5 patients in study 86-061, 2 patients in study 87-070 and 5 patients in study L0386g). The causes for withdrawal were primarily recurrence of intra-cranial tumour (5 cases). The rest of the withdrawals were due to precocious puberty (2 cases), seizures (2 cases), depression (1 case), rash (1 case) and recurrence of lymphoblastic leukaemia (1 case).

Deaths
No deaths were reported

Antibodies against GH
Prevalence of antibodies against growth hormone increased during the first 12 months of treatment. No additional increase in the prevalence was observed after 12 months. The antibody titers were generally low and efficacy of Nutropin did not seem to be influenced by the presence of antibodies.

Laboratory parameters
Except for well-known effects of growth hormone on thyroid parameters, protein and glucose metabolism, Nutropin did not cause any clinically significant changes in laboratory parameters.

- *Overall summary of safety concerning the indication CRI*

Exposure
Number of patients exposed to treatment as well as mean duration of exposure and number of patients years of exposure is listed in table.

Study	No of patients exposed	Mean duration of exposure (years)	No of patient years of exposure (years)
87-069	110	2.4	264
M0079g	48	1.0	48
Total	158	-	312

Adverse events
Adverse events possibly or probably related to Nutropin treatment were reported in four patients. In two cases hyperglycemia was found (whereas fasting glucose in a group of 50 patients on Nutropin did not change during 2 years). One case of pseudotumor cerebri with clear clinical symptoms was observed in which MRI scan was normal. However, other treatments for chronic renal insufficiency were possibly related to this event, and Nutropin therapy was continued in the patient. The last case was the patient with slipped femoral epiphysis described above. No cases of leukaemia, carpal tunnel syndrome, thyreoid dysfunction, or allergic reactions were reported.

Serious Adverse events
There were no reports of serious adverse events related to treatment.

Withdrawals
A total of 8 patients were withdrawn from treatment due to AEs. In study 87-069 7 patients discontinued treatment. Two patients on placebo stopped blinded treatment (precocious puberty and rapidly progression of renal failure). Five patients on Nutropin stopped blinded treatment (slipped femoral epiphysis, hip pain and incipient slipped femoral epiphysis, pulmonary oedema in congenital aortic stenosis, pancreatitis with insulin-dependent diabetes mellitus, and elevated SGOT/SGPT levels). In study M0079g one patient in the Nutropin treated group discontinued treatment due to a rash at the injection site. Relationship to treatment was judged as unclear.

Deaths
In study 87-069, two patients died due to complications related to renal transplantation. In study M079g, one patient in the control group died. The death was considered unrelated to treatment.

Antibodies against GH
In study 87-069, the incidence of patients with positive GH-antibodies was approximately 15%, and growth rates were unrelated to the presence of antibodies.

Laboratory parameters
There were no laboratory measurement abnormalities of clinical concern attributable to Nutropin treatment.

Renal function
Renal function as judged by serum creatinine and creatinine clearance decreased in both Nutropin and placebo treated children. There were no statistically significant differences between treatments.

- Summary of safety concerning the indication of growth retardation associated with Turner syndrome

Exposure
Safety was evaluated in 117 patients receiving Nutropin for an average of 4.6 years.

Adverse events
Adverse events were either common disorders of childhood or abnormalities known to be present in patients with Turner syndrome with increased incidence. No cases of leukaemia, slipped femoral epiphysis, pseudotumor cerebri, carpal tunnel syndrome, or diabetes were reported.

Serious Adverse events/Withdrawals
Three cases of serious adverse events/discontinuations occurred. One patient with a pre-existing seizure disorder developed hypoplastic anaemia. Her anticonvulsive therapy was considered responsible for the bone marrow suppression and was discontinued, while Nutropin continued without further events. One patient developed progressive right-side weakness and slurred speech after 44 months on Nutropin. She also received hormonal therapy in a cyclical regimen. All medication was discontinued, although the incident was not considered to be related to Nutropin. One patient discontinued due to an injection site reaction, which was later demonstrated to be related to allergy to the excipient.

Antibodies against GH
Antibodies to growth hormone was measured regularly during the study. The incidence of patients with positive GH-antibodies was ca 15%, and growth rates were unrelated to the presence of antibodies.

Baseline examinations in clinical trials of Turner syndrome and renal insufficiency have not demonstrated antibodies to GH prior to treatment in any subject. The applicant is unable to explain the mechanism of immunological reaction responsible for anti-GH antibody production other than ”some antibody response is common to most recombinant human protein therapeutics.” For children with congenital growth hormone deficiency this disorder is primarily a quantitative decrease in circulating GH (to concentrations below the diagnostic levels by stimulation tests), but very small amounts of hormone may be present.

Apparently, this fact is in many cases sufficient to induce such a tolerance in the immune system that exogenous administration of recombinant protein may not necessarily give rise to antibody formation.

- Overall summary of safety for the indication growth hormone deficiency in adults

Exposure

Number of patients exposed to treatment as well as mean duration of exposure and number of patients years of exposure is listed in the following table.

Study	No of patients exposed	Mean duration of exposure (months)	No of patient years of exposure (years)
M0431g	84	10.6	74
M0381g	43	14.6	53
Total	127	-	127

Adverse events

Compared to placebo, Nutropin treatment was associated with increased incidences of oedema, arthralgia/arthritis/arthrosis/joint disorder and tenosynovitis. These adverse events were mild-moderate and could be alleviated by dose reduction and continued treatment. No cases of leukaemia or pseudotumor cerebri were observed in the study.

Serious Adverse events

Serious adverse events were reported in 7 patients in the Nutropin group (3 recurrent CNS neoplasms, 1 squamous cell carcinoma, 1 myocardial infarction, 1 paravertebral cystic mass, and 1 breast mass with spontaneous remission) and in 3 patients in the placebo group (3 skin carcinomas). In all cases, the AE was considered to be remotely related to study medication.

Withdrawals

A total of 16 patients treated with Nutropin and 6 treated with placebo discontinued treatment as a result of adverse events. For the Nutropin treated subjects the reasons were carpal tunnel syndrome (4), arthritis like symptoms (4), weight gain/oedema (3), increasing supracellular mass (2), abnormal glucose tolerance test (1), Graves disease (1) and arthritis (1). For the placebo treated patients the reasons were recurrent brain lesion (2), arthritis (1), abnormal glucose tolerance test (1), traumatic injury (1), dyspnea (1)

Deaths

No deaths were reported during the study.

Antibodies against GH

One subject treated with Nutropin had a transient increase in antibody titer (from <1.0 to 1.2). After 12 months treatment, titers had reverted back to <1.0.

Laboratory parameters

I Apart from the well-known diabetogenic effect and mild increases of alkaline phosphatase, there were no clinically significant changes in laboratory test results.

Supporting studies

The potential influence on growth has been analysed in post-marketing protocols (NCGS). A major finding is that growth rates were not significantly different in patients treated with NutropinAq and Nutropin, indicating preserved biological activity. The company stresses that ”Antibodies to growth hormone were not associated with growth attenuation in any patient”, which may be a difficult conclusion to prove. Nevertheless, what has clearly been demonstrated is that the range of growth rates for antibody positive subjects did not differ from those for antibody negative subjects. It is considered that this result is the most important in the assessment of antibody impact.

From the NCGS data base 9,829 subjects are available for analysis as of 30 June 1999. 6,712 patients were exposed to Nutropion and 3,117 patients were exposed to NutropinAq. The total patient years contributed in the data base on NutropinAq were 3,161 years. In addition, the company has submitted a periodic safety update report on NutropinAq for the period 11 September 1999 to 5 July 2000.
The five most frequently reported adverse events were:

- Injection site pain (0.50%)
- Headache (0.16%)
- Scoliosis (0.16%)
- Intracranial hypertension (0.08%)
- Slipped capital femoral epiphysis (0.07%)

Other adverse events were observed very rarely, and the association with Nutropin therapy is difficult to assess (e.g. an incidence of diabetes mellitus of 0.05% in this childhood cohort of patients with an endocrine disorder probably is not significantly different from the background population).

From the NCGS database it is considered acceptable that no new and unexpected safety issues have been identified during the mentioned period, which would require an amendment of the SPC for NutropinAq.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

The currently available information demonstrates a sufficiently consistent production of NutropinAq and a well-defined quality, suitable for human use. The company has undertaken to provide the all outstanding data which remain as follow-up measures, listed in Chapter II.3, within the agreed time frame.

Preclinical pharmacology and toxicology

The pharmaco-toxicological dossier was considered an adequate documentation for NutropinAq.

The recommendations for SPC modification given from the pharmaco-toxicological perspective have been implemented.

In conclusion, the pharmacological-toxicological assessment is in favour of granting a marketing authorisation for NutropinAq.

Efficacy

Dose-response studies and main clinical studies
No formal dose-response studies were performed. Dosages used in the clinical trials as well as dosage recommendations in the SPC are based previous published studies of growth replacement. The clinical documentation is primarily based on trials with lyophilized Nutropin. Only one clinical trial with NutropinAq has been performed (study L0368g). However as NutropinAq can be considered bioequivalent with the lyophilized Nutropin formulations used in previous trials, the results obtained with lyophilized Nutropin can be extrapolated to NutropinAq.

Concerning the indication growth hormone deficiency in children, efficacy was not studied in placebo controlled experiments. Considering that growth hormone replacement therapy was a well established treatment in growth hormone deficient (GHD) children when the clinical development program was launched it would be unethical to perform placebo controlled trials.

Thus the lack of placebo-controlled studies is acceptable. In uncontrolled trials or in trials using Protropin (methionyl-growth hormone), Nutropin was shown to cause an improvement of growth, compared to baseline values. The magnitude was similar to the one observed for Protropin. Improvement of growth was maintained throughout treatment although, as with other recombinant growth hormones, the effect waned on prolonged treatment. Nevertheless, annual growth rates remained higher than baseline for at least 4 years. The improved growth was not accompanied by undue advancement of bone age. Predicted final adult height increased between 8 to 10 cm and the predicted final height standard deviation score (SDS) was between –0.4 and –0.9 indicating an average final height close to the mean of a healthy population. Actual final height data were not supplied but a conservative estimate for the end-point final height obtained at bone age >= 14 years for girls and >= 16 years for boys indicated that final height in boys was 171.7 cm with height SDS –0.7, which reflects satisfactorily growth improvement. For girls, the same figures are 154.5 cm final height with height SDS – 1.2. These end-points compare favorably with results obtained for the same indication with other brands of rhGH.

As regards the indication growth failure in children with CRI, two randomised, placebo-controlled studies have demonstrated that Nutropin (lyophilized) in addition to standard treatment of renal insufficiency significantly improves growth. After 24 months of treatment, height SDS improved between 0.8 and 1.3 in Nutropin treated patients whereas no change or slight deterioration in height SDS was observed in the placebo treated group. Correspondingly, predicted final height SD score improved in Nutropin treated children (from –1.6 at baseline to –1.0 and –0.8 after 12 and 24 months of treatment, respectively) whereas predicted final height remained unchanged in the placebo treated patients. Actual final height data were not supplied but this is acceptable as the majority of children with CRI undergo renal transplant before they reach final height.

Concerning the indication growth failure associated with Turners syndrome, a short term (1 year) placebo-controlled study have demonstrated that Nutropin improves growth rates compared to placebo. For once daily Nutropin, 3 times weekly Nutropin and placebo the growth rates were 8.1 , 6.7 and 4.0 cm/year respectively. After completion of the first year all subjects continued on Nutropin. Thus, only historical controls were available for the remainder of the study. Patients were followed until very close to final height. Improvement of final height compared to pre-treatment predicted final height was between 4.7 cm and 8.4 cm depending on age at initiation of treatment and time of initiation of oestrogen replacements (best results for early initiation of growth hormone therapy and late initiation of oestrogen therapy). For the historical controls actual final height was very close to the "pre-treatment" predicted final height (predicted final height at an age corresponding to the age of the actively treated patients at initiation of treatment).

In adults with GHD (both previously treated patients and naïve patients), placebo-controlled trials have demonstrated that Nutropin increases lean body mass and decreases total body fat. Compared to placebo, 12 months of Nutropin treatment increased total body % lean by 2.8 to 6.4 percentage points. Efficacy beyond 12 to 18 months was not investigated. Data on the effect of Nutropin on bone mineral density (BMD) were conflicting, with some studies showing an improvement of BMD while others showed no effect. As regards muscle strength, endurance, lipid profile and quality of life, Nutropin tended to improve some of the parameters but none of the differences attained statistical significance.

Safety

In children, Nutropin (lyophilized) was generally well tolerated with few adverse events. These were primarily of the type well known from other growth hormone products. No unexpected adverse events were encountered. As regards laboratory test results, no unexpected clinically significant abnormalities were encountered. As for other rhGH preparations, increased titres of antibodies were noted during the early phases of therapy. However, the frequency of antibodies to hGH was higher following NutropinAq compared to other hGH preparations on the market (after 24 months still 7% of the children with GHD). Therefor the frequency of antibodies to NutropinAq and possible effects on growth should be thoroughly investigated in post marketing studies.

In adults, Nutropin (lyophilized) was associated with the well-known side effects observed in previous trials with growth hormone replacement therapy in adults, primarily fluid accumulation and adverse events related to joints and bones. Apart from the well-known diabetogenic effect and an expected effect on alkaline phosphatase and thyroid parameters no clinically relevant abnormalities in the laboratory test results were encountered.

Benefit/risk assessment

Efficacy data indicate that NutropinAq improves growth in children with growth hormone deficiency or growth retardation due to chronic renal insufficiency or Turners syndrome. The safety profile of NutropinAq in children is generally comparable to what has been observed for previously approved recombinant human growth hormone products. However, limited data indicate that NutropinAq may be associated with a higher risk of development of antibodies against growth hormone. Provided that company commits to investigate the frequency of antibodies to NutropinAq and possible effects on efficacy (in a post-marketing study), the benefit-risk relation for NutropinAq in children can be considered positive. As regards the indication ”replacement in adults with GHD” the efficacy and safety of NutropinAq is similar to what has been reported for other recombinant human growth hormones. Thus, the benefit-risk balance for this indication must be considered acceptable.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of NutropinAq in the treatment of:

- long term treatment of children with growth failure due to a lack of adequate endogenous growth hormone secretion
- long-term treatment of growth failure associated with Turner syndrome
- treatment of children with growth failure associated with chronic renal insufficiency up to the time of renal transplantation
- replacement of endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult-onset etiology. Growth hormone deficiency should be confirmed appropriately prior to treatment.

was favourable and therefore recommended the granting of the marketing authorisation