PRODUCT INFORMATION

NutropinAq Cartridge Solution for Injection
Somatropin (rbe) 10 mg (5 mg/mL)

NAME OF THE MEDICINE

NutropinAq 10 mg (5 mg/mL) solution for injection in a cartridge.

One cartridge contains 10 mg (30 IU) of somatropin, recombinant DNA origin, *Escherichia coli*.

The CAS number is 12629-01-5.

DESCRIPTION

Somatropin is a human growth hormone (hGH) produced by recombinant DNA technology. Somatropin is a single-chain protein of 191 amino acids with a molecular weight of 22,125 daltons. Somatropin is synthesized in a specific laboratory strain of *E. coli* bacteria as a precursor consisting of the rhGH molecule preceded by the secretion signal from an *E. coli* protein. This precursor is then cleaved in the plasma membrane of the cell. The native protein is secreted into the periplasm where it is folded appropriately. The primary and secondary structures of somatropin are identical with pituitary-derived human growth hormone.

NutropinAq is supplied as a sterile solution with preservative for multiple use. The solution is nearly isotonic and has a pH of approximately 6.0.

PHARMACOLOGY

Pharmacotherapeutic group: Somatropin and analogues
ATC Code: H01 AC 01

Somatropin stimulates growth rate and increases adult height in children who lack endogenous growth hormone. Treatment of growth hormone deficient adults with somatropin results in reduced fat mass, increased lean body mass and increased spine bone mineral density was noted in some patient subgroups. Metabolic alterations in these patients include normalization of IGF-1 (insulin-like growth factor-I) serum levels.

In vitro and *in vivo* preclinical and clinical tests have demonstrated that somatropin is therapeutically equivalent to human growth hormone of pituitary origin.

Actions that have been demonstrated for human growth hormone include:

Tissue Growth
1. Skeletal growth: growth hormone and its mediator IGF-1 stimulate skeletal growth in growth hormone deficient children by an effect on the epiphyseal plates of long bones.

This results in a measurable increase in body length until these growth plates fuse at the end of puberty.
2. Cell growth: Treatment with somatropin results in an increase in both the number and size of skeletal muscle cells.
3. Organ growth: Growth hormone increases the size of internal organs, including kidneys, and increases red blood cell mass.

Protein metabolism
Linear growth is facilitated in part by growth hormone-stimulated protein synthesis. This is reflected by nitrogen retention as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen during growth hormone therapy.

Lipid metabolism
In GH-deficient patients, administration of GH resulted in lipid mobilisation, reduction in body fat stores, increased plasma fatty acids. A decrease in plasma cholesterol levels was noted in adult growth hormone deficient patients with childhood onset.

Carbohydrate metabolism
Patients with inadequate growth hormone secretion sometimes experience fasting hypoglycaemia that is improved by treatment with somatropin. Growth hormone therapy may decrease insulin sensitivity and impair glucose tolerance.

Mineral metabolism
Somatropin induces retention of sodium, potassium and phosphorus. Serum concentration of inorganic phosphorus are increased in patients with growth hormone deficiency after NutropinAq therapy due to metabolic activity associated with bone growth and increased tubular reabsorption in the kidney. Serum calcium is not significantly altered by somatropin. Adults with growth hormone deficiency show low bone mineral density and in the childhood-onset patient, NutropinAq has been shown to increase spine bone mineral density in a dose-dependent manner.

Connective tissue metabolism
Somatropin stimulates the synthesis of chondroitin sulphate and collagen as well as the urinary excretion of hydroxyproline.

Body composition
Adult growth hormone deficient patients treated with somatropin at a mean dosage of 0.014 mg/kg bodyweight daily demonstrate a decrease in fat mass and increase in lean body mass. When these alterations are coupled with the increase in total body water and bone mass, the overall effect of somatropin therapy is to modify body composition, an effect that is maintained with continued treatment.

Pharmacokinetics

General characteristics

The pharmacokinetic properties of NutropinAq have only been investigated in healthy adult males.

Absorption: The absolute bioavailability of recombinant human growth hormone after subcutaneous administration is about 80%.

Distribution: Animal studies with somatropin showed that growth hormone localises to highly perfused organs, particularly the liver and kidney. The volume of distribution at steady state for somatropin in healthy adult males is about 50 mL/kg bodyweight, approximating the serum volume.

Metabolism: Both the liver and the kidney have been shown to be important protein catabolising organs for growth hormone. Animal studies suggest that the kidney is the dominant organ of clearance. Growth hormone is filtered at the glomerulus and reabsorbed in the proximal tubules. It is then cleaved within renal cells into its constituent amino acids, which return to the systemic circulation.

Elimination: After subcutaneous bolus administration, the mean terminal half-life $t_{½}$ of somatropin is about 2.3 hours. After intravenous bolus administration of somatropin, the mean terminal half-life $t_{½}\beta$ or $t_{½}\gamma$ is about 20 minutes and the mean clearance is reported to be in the range of 116 - 174 mL/h/kg.

Available literature data suggest that somatropin clearance is similar in adults and children.

Clearance and mean terminal half-life $t_{½}$ of somatropin in adult and paediatric growth hormone deficient patients are similar to those observed in healthy subjects.

CLINICAL TRIALS

Paediatric Growth Hormone Deficiency (PGHD)

Two open label, uncontrolled multi-centre studies were performed in support of this indication. In one study, all patients (n=67) were previously untreated and in the other study, 63 patients were previously untreated and 9 children were previously treated with Nutropin. A dose of 0.043 mg/kg/day sc, was administered in both studies.

128/139 patients completed 12 months of therapy. Average treatment times were 3.2 and 4.6 years in the respective studies.

The primary efficacy variable was growth rate and in both studies there was a significant improvement in the naïve patients, increasing from 4.2 to 10.9 cm/year in one study and from 4.8 to 11.2 cm/year in the other at 12 months. The growth rate decreases after the first year in both studies, but continues to be greater than pre-treatment levels for up to 48 months treatment (7.1 cm/year). The data on height SDS improve each year over the whole period of the studies, increasing from -3.0 to -2.7 at baseline to -1.0 to -0.8 at Month 36.

The predicted adult height (PAH) was also used as a descriptive measure in these studies, and it increased from 157.7-161.0 cm at baseline to 161.4-167.4 cm at Month 12 and 166.2-171.1 cm at Month 36.

Adult Growth Hormone Deficiency (AGHD)

Two multi-centre, placebo-controlled, double blind studies in patients diagnosed with Adult Growth Hormone Deficiency were conducted.

One study was conducted in 166 subjects with adult-onset GHD, mean age 48.3 years, at doses of 0.0125 or 0.00625 mg/kg/day.

A second study was conducted in 64 previously treated subjects with childhood-onset GHD, mean age 23.8 years, at randomly assigned doses of 0.025 or 0.0125 mg/kg/day. The studies were designed to assess the effects of replacement therapy with GH on body composition and muscle strength or physical performance (co-primary endpoints).

In terms of body composition, in both studies Nutropin treatment resulted in significant changes ($p < 0.0001$) compared to placebo in total body % fat (-6.3 to -3.6 vs + 0.2 to -0.1), trunk % fat (-7.6 to -4.3 vs +0.6 to 0.0) and total body % lean (+3.6 to +6.4 vs -0.2 to +0.2). These changes were highly significant at the 12-month time point in both studies.

Muscle strength and physical endurance were not markedly abnormal at baseline, and no statistically significant effects of Nutropin therapy were observed in the two studies.

Changes in LDL cholesterol and LDL:HDL ratio, and evaluation of Bone Mineral Density were secondary endpoints of the studies. In the adult-onset study, significant decreases from baseline to Month 12 in LDL cholesterol and LDL:HDL ratio were seen in the Nutropin group compared to the placebo group, $p < 0.02$. In the childhood-onset study, significant decreases from baseline to Month 12 in total cholesterol, LDL cholesterol, and LDL:HDL ratio were seen in the high-dose Nutropin group only, compared to the placebo group, $p < 0.05$.

No significant changes in BMD were observed in this cohort of adult-onset AGHD patients. In the childhood-onset study, a special statistical analysis of the data concluded that at 24 months all groups had an increase in BMD from baseline, although there was no statistically significant dose response for total body BMD. Lumbar spine BMD had statistically significant increases in both treated groups and the increase was dose dependent.

In both studies, Quality of Life assessments were generally normal at baseline and did not improve through treatment.

Effects of Nutropin on Growth Failure associated with Chronic Renal Insufficiency (CRI)

Data is presented from two multi-centre, controlled studies conducted for 2 years and followed by an open label uncontrolled extension. In both studies, Nutropin (formulation without polysorbate 20) at a dose of 0.05 mg/kg/day sc, was used.

128 patients received Nutropin over the 24 month controlled phase of the studies and 139 patients were treated with Nutropin in the open extension phases. The primary endpoints were growth rate and change in height SDS.

In both studies, a significant increase in growth rate compared to placebo was seen over the first 12 months treatment period (9.1-10.9 cm/yr vs 6.2-6.6 cm/yr), which decreased slightly in the second year (7.4-7.9 cm/yr vs 5.5-6.6 cm/yr). In both studies, there was also a significant increase in height SDS in the Nutropin groups in comparison to placebo or untreated group, from -2.9 SDS to -1.4 SDS at month 24 in Nutropin group versus no change in height SDS in placebo group (-2.8 to -2.9 SDS), and from -2.9 to -1.9 SDS at month 12 in Nutropin group versus no change in untreated group. A total of 58% and 65% of Nutropin treated patients who were below normal range at baseline, had reached heights within the normal range by Month 24 in the two studies.

A statistically significant increase in Predicted Adult Height SDS was observed in the Nutropin groups of both studies, from -1.6 or -1.7 at baseline to -0.7 or -0.9 at Month 24. This continued to increase in those patients treated for 36 and 48 months.

IGF-I levels, which were low in the patients recruited into the studies, were restored to within the normal range with Nutropin therapy.

Turner Syndrome

117 patients were treated in a multi-centre, open label, controlled study. 36/117 received Nutropin 0.0125 mg/kg three times a week (TIW) with an average treatment time of 4.7 years. 81/117 received 0.054 mg/kg Nutropin daily with an average treatment time of 4.6 years. Patients under 11 years of age were also randomized to receive oestrogen therapy, either in late (15 years) or early (12 years) adolescence.

The primary efficacy variable was adult height. Growth rate in treated patients increased significantly from 3.6-4.1 cm/year at baseline to 6.7-8.1 cm/year at Month 12, 6.7-6.8 cm/year at Month 24 and 4.5-5.1 cm/year at Month 48. This was accompanied by a significant increase in Turner height SDS from -0.1 to 0.5 at baseline to 0.0 to 0.7 at Month 12 and 1.6 to 1.7 at Month 48.

Nutropin conferred substantial increases in growth compared to historical controls in all groups. A consistently more rapid advance of bone age was seen in the early, than in the late oestrogen group.

INDICATIONS

- 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,

- Treatment of adults with severe growth hormone deficiency as diagnosed in the insulin tolerance test for growth hormone deficiency and defined by peak GH concentrations of less than 2.5 ng/mL.

CONTRAINDICATIONS

Hypersensitivity to somatropin or to any of the excipients.

Somatropin should not be used for growth promotion in patients with closed epiphyses.

Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial lesions must be inactive and antitumour therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open-heart or abdominal surgery, multiple accidental traumas or to treat patients having acute respiratory failure.

PRECAUTIONS

The maximum recommended daily dose should not be exceeded. (see "*Dosage and Administration*")

In adults with growth hormone deficiency the diagnosis should be established depending on the etiology:

Adult-onset: The patient must have growth hormone deficiency as a result of hypothalamic or pituitary disease, and at least one other hormone deficiency diagnosed (except for prolactin). Test for growth hormone deficiency should not be performed until adequate replacement therapy for other hormone deficiencies have been instituted.

Childhood-onset: Patients who have had growth hormone deficiency as a child should be retested to confirm growth hormone deficiency in adulthood before replacement therapy with NutropinAq is started.

In patients with previous malignant disease, special attention should be given to signs and symptoms of relapse.

Patients with pre-existing tumours or growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the lesion. In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumours, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms.

NutropinAq is not indicated for the long term treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome, unless they also have a diagnosis of growth hormone deficiency. There have been reports of sleep apnoea and sudden death after initiating therapy with growth hormone in paediatric patients with

Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

The effects of growth hormone on recovery were studied in two placebo-controlled clinical trials involving 522 adult patients who were critically ill due to complications following open-heart or abdominal surgery, multiple accidental traumas, or who were having acute respiratory failure. Mortality was higher (41.9 % vs. 19.3 %) among growth hormone treated patients (doses 5.3 - 8 mg/day) compared to those receiving placebo.

The safety of continuing somatropin treatment in patients with acute critical illness in intensive care units due to complications following open-heart or abdominal surgery, multiple accidental trauma or acute respiratory failure receiving replacement doses for approved indications has not been established. Therefore, the benefit-risk assessment for continuing treatment should be performed carefully.

Patients with growth hormone failure secondary to chronic renal insufficiency should be examined periodically for evidence of progression of renal osteodystrophy.

Paediatric patients with advanced renal osteodystrophy or endocrine disorders, including growth hormone deficiency, have a higher incidence of slipped capital femoral epiphyses and aseptic necrosis of the femoral head. Physicians and parents should be alert to the development of a limp or complaints of hip or knee pain in patients treated with NutropinAq. Any patient with the onset of a limp or complaint of hip or knee pain should be evaluated.

Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment.

Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the insulin dose may require adjustment after NutropinAq therapy is instituted. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy. NutropinAq therapy is not indicated in diabetic patients with active proliferative or severe non-proliferative retinopathy.

Intracranial hypertension with papilloedema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with somatropin. Symptoms usually occur within the first eight weeks of the initiation of NutropinAq therapy. In all reported cases, intracranial hypertension-associated signs and symptoms resolved after reduction of the somatropin dose or termination of the therapy. Funduscopic examination is recommended at the initiation and periodically during the course of treatment.

Hypothyroidism may develop during treatment with somatropin, and untreated hypothyroidism may prevent optimal response to NutropinAq. Therefore, patients should have periodic thyroid function tests and should be treated with thyroid hormone when indicated. Patients with severe hypothyroidism should be treated accordingly prior to the start of NutropinAq therapy.

Leukaemia has been reported in a small number of GHD patients treated with GH. A causal relationship to somatropin therapy has not been established.

Children treated with somatropin have an increased risk of developing pancreatitis compared to adults treated with somatropin. Although rare, pancreatitis should be considered in somatropin-treated children who develop abdominal pain

Since somatropin therapy following renal transplantation has not been adequately tested, NutropinAq treatment should be terminated after that surgery.

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth. The use of NutropinAq in patients with chronic renal insufficiency receiving glucocorticoid therapy has not been evaluated.

Effects on fertility

The effects of NutropinAq on fertility have not been assessed in animal studies. Somatropin is known to be associated with inhibition of reproduction in male and female rats at doses of 3 IU/kg/day (1 mg/kg/day) or more, with reduced copulation and conception rates, lengthened or absent oestrous cycles, and at 10 IU/kg/day (3.3 mg/kg/day), a lack of responsiveness of females to males, and slight reductions in sperm motility and survival. Rat reproduction was unaffected by 1 IU/kg/day (0.3 mg/kg/day) somatropin, which resulted in a systemic exposure (based on body surface area) of approximately twice that anticipated at the maximum clinical dose in adult patients.

Carcinogenicity

The carcinogenicity potential of NutropinAq has not been investigated in long-term animal studies. Somatropin raises the serum levels of IGF-1. Associations between elevated serum IGF-1 concentrations and risk of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somatropin who do not have growth hormone deficiency and who are treated for prolonged periods, is not known.

Genotoxicity

Mutagenicity studies have not been conducted with NutropinAq. In studies with other recombinant human growth hormone preparations, there was no evidence of gene mutation in bacterial reverse mutations assays, chromosal damage in human lymphocytes and rat or mouse bone marrow cells, gene conversion in yeast or unscheduled DNA synthesis in human carcinoma cells.

Use in Pregnancy (Category B2)

Animal reproductive studies have not been conducted with NutropinAq. It is not known whether NutropinAq can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Another form of recombinant human growth hormone

was not teratogenic in rats or rabbits at respective doses of up to 15 and 28 times the maximum recommended clinical dose based on body surface area. In rats, recombinant human growth hormone administered from late gestation to weaning, at 15 times the clinical dose based on body surface area, was associated with increased bodyweight of pups at birth and postnatally.

Because animal studies are not always predictive of human response, NutropinAq should be discontinued if pregnancy occurs.

Use in Lactation

No study has been conducted with NutropinAq in breastfeeding women and it is not known whether somatropin is excreted in human milk. Following subcutaneous administration of radiolabelled recombinant human growth hormone to lactating rats, radioactivity was found in the milk reaching four times the concentration in maternal plasma. However, absorption of intact protein from the gastrointestinal tract of the infant is unlikely.

Interactions with other drugs

Limited published data indicate that growth hormone treatment increases cytochrome P450 mediated antipyrine clearance in man. Monitoring is advisable when NutropinAq is administered in combination with drugs known to be metabolised by CYP450 liver enzymes, such as corticosteroids, sex steroids, anticonvulsants, and cyclosporin.

In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of somatropin treatment.

Use in the elderly

Clinical studies of NutropinAq did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Use in Patients with Renal Impairment

Children and adults with chronic renal failure and end-stage renal disease tend to have decreased clearance compared to normal subjects. Endogenous growth hormone production may also increase in some individuals with end-stage renal disease. However, no somatropin accumulation has been reported in children with chronic renal failure or end-stage renal disease dosed with current regimens.

Limited published data for exogenously-administered somatropin suggest absorption and elimination half-lives and time of maximum concentration t_{max} in Turner patients are similar to those observed in both normal and growth hormone deficient populations.

Use in Patients with Hepatic Impairment

In patients with severe liver dysfunction a reduction in somatropin clearance has been noted. The clinical significance of this decrease is unknown.

Effects on ability to drive and use machines

No studies on the effects of NutropinAq on the ability to drive and use machines have been performed. Somatropin has no known effect on the ability to drive or to use machines.

ADVERSE EFFECTS

The adverse reactions reported in both adults and children receiving Nutropin or NutropinAq are listed in the tables below, based on experience from clinical trials in all approved indications (642 patients) and a post-marketing surveillance survey (National Cooperative Growth Study [NCGS] in 35,344 patients). Approximately 2.5% of patients from the NCGS have experienced drug related adverse reactions, with most of these adverse reactions being reported in the "general disorders and administration site conditions" system organ class.

In addition, indication-specific adverse reactions from the same clinical trials are listed in the text below the tables.

Within the system organ classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10), common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions observed in Clinical Trials

System Organ Class	Reactions observed in Pivotal and Supportive Clinical Trials (in 642 patients)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon: Neoplasm malignant, neoplasm benign
Blood and lymphatic system disorders	Uncommon: Anaemia
Endocrine disorders	Common: Hypothyroidism
Metabolism and nutrition disorders	Common: Glucose tolerance impaired Uncommon: Hypoglycaemia, hyperphosphatemia
Psychiatric disorders	Uncommon: Personality disorder
Nervous system disorders	Common: Headache, hypertonia Uncommon: Carpal tunnel syndrome, somnolence, nystagmus
Eye disorders	Uncommon: Papilloedema, diplopia
Ear and labyrinth disorders	Uncommon: Vertigo
Cardiac disorders	Uncommon: Tachycardia
Vascular disorders	Uncommon: Hypertension
Gastrointestinal disorders	Uncommon: Abdominal pain, vomiting, nausea, flatulence

Skin and subcutaneous tissue disorders	Uncommon: Exfoliative dermatitis, skin atrophy, skin hypertrophy, hirsutism, lipodystrophy, urticaria
Musculoskeletal and connective tissue disorders	Very common in adults, common in children: Arthralgia, myalgia Uncommon: Muscle atrophy, bone pain
Renal and urinary disorders	Uncommon: Urinary incontinence, pollakiuria, polyuria, urine abnormality
Reproductive system and breast disorders	Uncommon: Uterine haemorrhage, genital discharge
General disorders and administration site conditions	Very common in adults, common in children: Peripheral oedema, oedema Common: Asthenia, injection site reaction Uncommon: Injection site haemorrhage, injection site atrophy, injection site mass, hypertrophy
Investigations	Common: Drug specific antibody present

Table 2: Adverse reactions observed in the post-marketing environment

System Organ Class	**Reactions observed from the post-marketing environment**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare: Neoplasm malignant recurrence, melanocytic naevus
Endocrine disorders	Rare: Hypothyroidism
Metabolism and nutrition disorders	Rare: Diabetes mellitus, hyperglycaemia, hypoglycaemia, glucose tolerance impaired
Psychiatric disorders	Rare: Abnormal behaviour, depression, insomnia
Nervous system disorders	Uncommon: Headache Rare: Benign intracranial hypertension, intracranial pressure increased, migraine, carpal tunnel syndrome, paraesthesia, dizziness
Eye disorders	Rare: Papilloedema, vision blurred
Vascular disorders	Rare: Hypertension
Respiratory, thoracic and mediastinal disorders	Rare: Tonsillar hypertrophy Uncommon: Adenoidal hypertrophy
Gastrointestinal disorders	Rare: Abdominal pain, diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Rare: Generalised pruritus, urticaria,rash
Musculoskeletal and connective tissue disorders	Uncommon: Epiphysiolysis, scoliosis progression, arthralgia Rare: Bone development abnormal, osteochondrosis, muscular weakness, pain in extremity
Reproductive system and breast disorders	Rare: Gynaecomastia
General disorders and administration site conditions	Uncommon: Peripheral oedema, oedema, injection site reaction (irritation, pain) Rare: Asthenia, face oedema, fatigue, irritability, pain, pyrexia, injection site reaction (haemorrhage, haematoma, atrophy, urticaria, pruritus, swelling, erythema)
Investigations	Rare: Blood glucose increased, weight increased

Indication-specific adverse drug reactions from clinical trials

Paediatric patients

Patients with growth failure due to inadequate growth hormone secretion (n=236)
Common: CNS neoplasm (2 patients experienced a recurrent medulloblastoma, 1 patient experienced a histiocytoma)

Patients with growth failure associated with Turner syndrome (n=l08)
Common: Menorrhagia
Patients with growth failure associated with chronic renal insufficiency (n=l71)
Common: Renal failure, peritonitis, osteonecrosis, blood creatinine increase

Adult patients:
Adults with growth hormone deficiency (n=127)
Very common: Paraesthesia
Common: Hyperglycaemia, hyperlipidaemia, insomnia, synovial disorder, arthrosis, muscular weakness, back pain, breast pain, gynaecomastia

Patients with endocrinological disorders are more prone to develop an epiphysiolysis.

As with all recombinant proteins, a small percentage of patients may develop antibodies to the protein somatropin. The binding capacity of growth hormone antibodies was lower than 2 mg/L in NutropinAq subjects tested, which has not been associated with adversely affected growth rate.

DOSAGE AND ADMINISTRATION

Recommended Dosage:
Growth failure in children due to inadequate growth hormone secretion:
0.025 - 0.035 mg/kg bodyweight given as a daily subcutaneous injection.

Growth failure associated with Turner syndrome:
Up to 0.05 mg/kg bodyweight given as a daily subcutaneous injection.

Growth failure associated with chronic renal insufficiency:
Up to 0.05 mg/kg bodyweight given as a daily subcutaneous injection.
Somatropin therapy may be continued up to the time of renal transplantation.

Growth hormone deficiency in adults:

At the start of somatropin therapy, low initial doses of 0.15 - 0.3 mg are recommended, given as a daily subcutaneous injection. The dose should be adjusted stepwise, controlled by serum Insulin-Like Growth Factor-1 (IGF-1) values. The recommended final dose seldom exceeds 1.0 mg/day. In general, the lowest efficacious dose should be administered. In older or overweight patients, lower doses may be necessary.

Administration
The solution for injection should be administered subcutaneously each day in the upper arm, abdomen or thigh. The site of injection should be changed. *The product is for use in one individual only*.

NutropinAq is supplied as a sterile solution with preservative for multiple use. The solution should be clear immediately after removal from the refrigerator. If the solution is cloudy, the content must not be injected. Gently swirl. Do not shake vigorously in order not to denature the protein.

NutropinAq is intended for use only with the NutropinAq Pen. Wipe the rubber seal of the NutropinAq with rubbing alcohol or an antiseptic solution to prevent contamination of the contents by microorganisms that may be introduced by repeated needle insertions. It is recommended that NutropinAq be administered using sterile, disposable needles.

The NutropinAq Pen allows for administration of a minimum dose of 0.1 mg to a maximum dose of 4.0 mg, in 0.1 mg increments.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

Acute overdose could lead to hyperglycaemia. Long-term overdose could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone.

PRESENTATION AND STORAGE CONDITIONS

2 mL of solution in a cartridge (Type I glass) closed with a stopper (butyl rubber) and a seal (rubber). Excipients: sodium chloride, phenol, polysorbate 20, sodium citrate and citric acid anhydrous, water for injections.
Pack sizes of 1 and 3 cartridges.

Storage

Store at 2°C - 8°C. Do not freeze.
Keep the container in the outer carton. Protect from light.
A cartridge that is in the pen should not be removed during injections.

Chemical and physical in-use stability has been demonstrated for 28 days at 2°C - 8°C.

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2°C - 8°C. The NutropinAq is designed to withstand a nominal (one hour maximum) period of time outside of the refrigerator on a daily basis. Do not remove the cartridge that is being used from the NutropinAq Pen between injections.

After first opening: the product may be stored for up to 28 days at 2°C - 8°C.

POISON SCHEDULE OF THE DRUG: S4

NAME AND ADDRESS OF THE SPONSOR

Ipsen Pty Ltd
Level 2, Building 4, Brandon Office Park
540 Springvale Road
Glen Waverley Victoria 3150

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