

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NutropinAq 10 mg/2 ml (30 IU) solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 5 mg of somatropin*

One cartridge contains 10 mg (30 IU) of somatropin

* Somatropin is a human growth hormone produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paediatric population

- Long-term treatment of children with growth failure due to inadequate endogenous growth hormone secretion.
- Long-term treatment of girls from 2 years old with 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.

Adult population

- 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.
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.

4.2 Posology and method of administration

Diagnosis and therapy with somatropin should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with the therapeutic indication of use.

Posology

The NutropinAq dosage and administration schedule should be individualised for each patient.

Paediatric population

Growth failure in children due to inadequate growth hormone secretion

0.025 - 0.035 mg/kg bodyweight given as a daily subcutaneous injection.

Somatropin therapy should be continued in children and adolescents until their epiphysis are closed.

Growth failure associated with Turner syndrome

Up to 0.05 mg/kg bodyweight given as a daily subcutaneous injection.

Somatropin therapy should be continued in children and adolescents until their epiphysis are closed.

Growth failure associated with chronic renal insufficiency

Up to 0.05 mg/kg bodyweight given as a daily subcutaneous injection.

Somatropin therapy should be continued in children and adolescents until their epiphysis are closed, or up to the time of renal transplantation.

Adult population

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-I) 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.

Women may require higher doses than men, with men showing an increasing IGF-I sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen therapy, are under-treated while men are over-treated.

Method of administration

The solution for injection should be administered subcutaneously each day. The site of injection should be changed.

Precaution to be taken before manipulating or administering the product

NutropinAq is supplied as a multi-dose solution. After removal from the refrigerator, if the solution is cloudy, the content must not be injected. Gently swirl. Do not shake vigorously as it could denature the protein. NutropinAq is intended for use only with the NutropinAq Pen.

For instructions for use and handling of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. 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 tumours 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.

4.4 Special warnings and precautions for use

The maximum recommended daily dose should not be exceeded (see section 4.2).

Neoplasm

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

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

Prader-Willi syndrome

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.

Acute critical illness

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.

Chronic renal insufficiency

Patients with growth hormone failure secondary to CRI should be examined periodically for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphyses and aseptic necrosis of the femoral head may be seen in children with advanced renal osteodystrophy and in growth hormone deficiency, and it is uncertain whether these problems are affected by GH therapy.

Slipped capital femoral epiphysis

In patients with endocrine disorders, including growth hormone deficiency, slipped epiphyses of the hip may occur more frequently than in the general population. A patient treated with somatropin who develops a limp or complains of hip or knee pain should be evaluated by a physician.

Scoliosis

Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during treatment. However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis.

Glycaemic control

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. Somatropin therapy is not indicated in diabetic patients with active proliferative or severe non-proliferative retinopathy.

Intracranial hypertension

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. Funduscopy examination is recommended at the initiation and periodically during the course of treatment.

Hypothyroidism

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.

Renal transplantation

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

Glucocorticoids use

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of NutropinAq. 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.

Leukaemia

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

Pancreatitis

Although rare, pancreatitis should be considered in somatropin-treated patients who develop abdominal pain, especially in children.

Use with oral oestrogen therapy

If a woman taking NutropinAq begins oral oestrogen therapy, the dose of NutropinAq may need to be increased to maintain the serum IGF-1 levels within the normal age appropriate range. Conversely, if a woman on NutropinAq discontinues oral oestrogen therapy, the dose of NutropinAq may need to be reduced to avoid excess of growth hormone and/or side effects (see section 4.5).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per cartridge, i.e. essentially "sodium-free".

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

Limited published data indicate that growth hormone treatment increases cytochrome P450 mediated antipyrine clearance in man. Monitoring is advisable when somatropin is administered in combination with medicinal products 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 (see section 4.4).

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral hypoglycemic medicinal product may require adjustment when somatropin therapy is initiated (see section 4.4).

In women on oral oestrogen replacement, a higher dose of growth hormone may be required to achieve the treatment goal (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of somatropin in pregnant women. Thus, the risk for humans is unknown.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Somatropin is not recommended during pregnancy and should be discontinued if pregnancy occurs.

During pregnancy, maternal somatropin will largely be replaced by placental growth hormone.

Breast-feeding

It is unknown whether somatropin/metabolites are excreted in human milk. No animal data are available.

Caution should be exercised while breast-feeding during treatment with NutropinAq.

Fertility

The effect of NutropinAq has not been assessed in conventional animal fertility studies (see section 5.3) or clinical studies.

4.7 Effects on ability to drive and use machines

Somatropin has no known effect on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions reported in both adults and children receiving Nutropin, NutropinAq, Nutropin Depot or Protropin (somatrem) are listed in the table below, based on experience from clinical trials all approved indications (642 patients) and post-marketing sources which included a 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.

The most frequently reported adverse reactions from the pivotal and supportive clinical trials were hypothyroidism, impaired glucose tolerance, headache, hypertonia, arthralgia, myalgia, peripheral oedema, oedema, asthenia, injection site reaction and the presence of drug specific antibodies.

The most serious adverse reactions from the pivotal and supportive clinical trials were neoplasm and intracranial hypertension.

Neoplasms (malignant and benign) were reported in both the pivotal and supportive clinical trials and in the post-marketing surveillance survey (see sections 4.3 and 4.4). The majority of neoplasms reported were recurrence of previous neoplasms and second neoplasms.

Intracranial hypertension was reported in the post-marketing surveillance survey. It is typically associated with papilloedema, visual changes, headache, nausea, and/or vomiting and symptoms usually occur within eight weeks of initiation of therapy with NutropinAq.

NutropinAq reduces insulin sensitivity; glucose tolerance impairment was reported in both the pivotal and supportive clinical trials and the post-marketing surveillance survey. Events of diabetes mellitus and hyperglycaemia were reported in the post-marketing surveillance survey (see section 4.4).

Injection site reactions such as haemorrhage, atrophy, urticaria and pruritus were reported in the pivotal and supportive clinical trials and/or the post-marketing surveillance survey. These events can be avoided by correct injection technique and rotation of injection sites.

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.

Tabulated summary of adverse reactions

Table 1 contains very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$) adverse reactions which occurred in clinical trials and a post-marketing surveillance survey. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Other adverse reactions have been identified during post approval use of NutropinAq. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

System Organ Class	Reactions observed in Pivotal and Supportive Clinical Trials (in 642 patients)	Reactions observed from the post marketing environment
Neoplasms benign, malignant and unspecified (including cysts and polyps)	<u>Uncommon</u> : Neoplasm malignant, neoplasm benign	<u>Rare</u> : Neoplasm malignant recurrence, melanocytic naevus
Blood and lymphatic system disorders	<u>Uncommon</u> : Anaemia	
Endocrine disorders	<u>Common</u> : Hypothyroidism	<u>Rare</u> : Hypothyroidism
Metabolism and nutrition disorders	<u>Common</u> : Glucose tolerance impaired <u>Uncommon</u> : Hypoglycaemia, hyperphosphatemia	<u>Rare</u> : Diabetes mellitus, hyperglycaemia, hypoglycaemia, glucose tolerance impaired
Psychiatric disorders	<u>Uncommon</u> : Personality disorder	<u>Rare</u> : Abnormal behaviour, depression, insomnia
Nervous system disorders	<u>Common</u> : Headache, hypertonia, <u>Uncommon</u> : Carpal tunnel syndrome, somnolence, nystagmus	<u>Uncommon</u> : Headache <u>Rare</u> : Benign intracranial hypertension, intracranial pressure increased, migraine, carpal tunnel syndrome, paraesthesia, dizziness
Eye disorders	<u>Uncommon</u> : Papilloedema, diplopia	<u>Rare</u> : Papilloedema, vision blurred
Ear and labyrinth disorders	<u>Uncommon</u> : Vertigo	
Cardiac disorders	<u>Uncommon</u> : Tachycardia	
Vascular disorders	<u>Uncommon</u> : Hypertension	<u>Rare</u> : Hypertension
Respiratory thoracic and mediastinal disorders		<u>Rare</u> : Tonsillar hypertrophy <u>Uncommon</u> : Adenoidal hypertrophy
Gastrointestinal disorders	<u>Uncommon</u> : Abdominal pain, vomiting, nausea, flatulence	<u>Rare</u> : Abdominal pain, diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	<u>Uncommon</u> : Exfoliative dermatitis, skin atrophy, skin hypertrophy, hirsutism, lipodystrophy, urticaria	<u>Rare</u> : Generalised pruritus, urticaria, rash
Musculoskeletal and connective tissue disorders	<u>Very common in adults, common in children</u> : Arthralgia, myalgia <u>Uncommon</u> : Muscle atrophy, bone pain	<u>Uncommon</u> : Slipped capital femoral epiphysis, scoliosis progression, arthralgia <u>Rare</u> : Bone development abnormal, osteochondrosis, muscular weakness, pain in extremity
Renal and urinary disorders	<u>Uncommon</u> : Urinary incontinence, pollakiuria, polyuria, urine abnormality	

Reproductive system and breast disorders	<u>Uncommon</u> : Uterine haemorrhage, genital discharge	<u>Uncommon</u> : Gynaecomastia
General disorders and administration site conditions	<u>Very common in adults, common in children</u> : Peripheral oedema, oedema <u>Common</u> : Asthenia, injection site reaction <u>Uncommon</u> : Injection site haemorrhage, injection site atrophy, injection site mass, hypertrophy	<u>Uncommon</u> : Peripheral oedema, oedema, injection site reaction (irritation, pain) <u>Rare</u> : Asthenia, face oedema, fatigue, irritability, pain, pyrexia, injection site reaction (haemorrhage, haematoma, atrophy, urticaria, pruritus, swelling, erythema)
Investigations	<u>Common</u> : Drug specific antibody present	<u>Rare</u> : Blood glucose increased, weight increased

Description of selected adverse reactions

Neoplasm

There is a risk of neoplasia due to treatment with GH. The underlying risk varies according to the underlying cause for growth hormone deficiency (e.g. secondary to intracranial lesion), associated co-morbidities and treatment(s) undertaken. NutropinAq therapy must not be initiated when there is evidence of tumour activity. Patients with pre-existing tumours or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. Treatment must be discontinued if there is evidence of tumour growth.

Intracranial hypertension

In all reported cases, intracranial hypertension associated signs and symptoms resolved after reduction of the NutropinAq dose or termination of therapy (see section 4.4). Fundoscopic examination is recommended at the initiation and periodically during the course of treatment.

Hypothyroidism

Hypothyroidism may develop during treatment with NutropinAq and untreated hypothyroidism may prevent optimal response to NutropinAq. Patients should have periodic thyroid function tests and should be treated with thyroid hormone when required. Patients with pre-existing hypothyroidism should be treated prior to the start of NutropinAq therapy.

Glycaemic control

As NutropinAq may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the dose of insulin may need adjustment after NutropinAq therapy is initiated. Patients with diabetes or glucose intolerance should be monitored closely during somatotropin therapy.

Injection site reactions

Injection site reactions may be avoided by using the correct injection technique and rotation of injection sites.

Slipped capital femoral epiphysis

Patients with endocrinological disorders are more prone to develop a slipped capital femoral epiphysis.

Indication-specific adverse drug reactions from clinical trials

Paediatric population

Children with growth failure due to inadequate growth hormone secretion (n=236)

Common: central nervous system neoplasm (2 patients experienced a recurrent medulloblastoma, 1 patient experienced a histiocytoma). See also section 4.4.

Girls with growth failure associated with Turner syndrome (n=108)

Common: menorrhagia.

Children with growth failure associated with chronic renal insufficiency (n=171)

Common: renal failure, peritonitis, osteonecrosis, blood creatinine increase. Children with chronic renal insufficiency receiving NutropinAq are more likely to develop intracranial hypertension, although children with organic GHD and Turner syndrome also have an increased incidence. The greatest risk is at the beginning of treatment.

Adult population

Adults with growth hormone deficiency (n=127)

Very common: paraesthesia.

Common: hyperglycaemia, hyperlipidaemia, insomnia, synovial disorder, arthrosis, muscular weakness, back pain, breast pain, gynaecomastia.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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.

Management

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, Somatropin and analogues, ATC Code: H01 AC 01

Mechanism of action

Somatropin stimulates growth rate and increases adult height in children who lack endogenous growth hormone and in children who have growth failure due to Turner Syndrome or CRI. Treatment of growth hormone deficient adults with somatropin results in reduced fat mass, increased lean body mass and increased spine bone mineral density. Metabolic alterations in these patients include normalisation of IGF-I serum levels.

Pharmacodynamic effects

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-I 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 somatotropin 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.

Carbohydrate metabolism

Patients with inadequate growth hormone secretion sometimes experience fasting hypoglycaemia that is improved by treatment with somatotropin. 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 somatotropin. 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 somatotropin 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 somatotropin therapy is to modify body composition, an effect that is maintained with continued treatment.

Clinical efficacy and safety

Growth failure in children

Two pivotal, open label, uncontrolled, multicentre studies have been conducted, one exclusively in previously untreated patients (n=67), and the other in previously untreated patients (n=63) and in children previously treated with somatotropin (n=9). The dose in both studies was 0.043 mg/kg/day, administered subcutaneously (s.c.). Doses used in these US based studies are consistent with the US approved dose regimen. Of the 139 patients included, 128 completed the first 12 months of therapy, with an average treatment time of 3.2 and 4.6 years and a total exposure of 542 patient years. In both studies there was a significant improvement in growth rate 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 decreased after the first year in both studies, but continued to be greater than pretreatment levels for up to 48 months treatment (7.1 cm/year). The height standard deviation score (SDS) improved each year, increasing from -3.0 to -2.7 at baseline to -1.0 to -0.8 at Month 36. The improvements in growth were not accompanied by undue advancement of bone age, which would jeopardise future growth potential. Predicted adult height (PAH) 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.

Supportive data are provided by two other studies, in which patients were given a dose of 0.3 or 0.6 mg/kg/week either as a daily injection or three times per week, or 0.029 mg/kg/day. The

data on growth rate and height SDS were broadly similar to those observed in the pivotal studies.

For 51 patients who achieved near-adult height after an average duration of treatment of 6 years in males and 5 years in females, the mean near-adult height SDS was -0.7 in males and -1.2 in females.

IGF-I levels increased from a baseline of 43 ng/ml to 252 ng/ml at 36 months, which approximate to the normal levels expected in children of this age.

The most common adverse events (AEs) observed in the pivotal studies were infection, headache, otitis media, fever, pharyngitis, rhinitis and gastroenteritis and vomiting.

Growth failure associated with chronic renal insufficiency

Two pivotal, multicentre, controlled studies have been conducted in patients with growth failure associated with chronic renal insufficiency (CRI). Each study had a two year treatment period which included a placebo arm, followed by an open label uncontrolled extension in which all patients received somatropin. The dose was 0.05 mg/kg/day s.c. in both studies. The results of both studies were similar.

In total, 128 patients received somatropin over the 24 month controlled phase of the 2 studies, and 139 patients were treated with somatropin in the open extension phases. Overall, 171 patients were exposed to somatropin for an average of 3.5 or 2.8 years.

Both studies demonstrated a statistically significant increase in growth rate compared to placebo over the first year (9.1-10.9 cm/year vs 6.2-6.6 cm/year), which decreased slightly in the second year (7.4-7.9 cm/year vs 5.5-6.6 cm/year). There was also a significant increase in height SDS in somatropin-treated patients, from -2.9 to -2.7 at baseline to -1.6 to -1.4 at 24 months. Height gains were maintained in the patients treated for 36 or 48 months. A total of 58% and 65% of somatropin-treated patients, who were below normal range at baseline, had reached heights within the normal range by Month 24.

The results to Month 60 show continued improvement, and more patients reached height SDS in the normal range. The average change in height SDS after 5 years of treatment was close to 2 standard deviations (SDs). A statistically significant increase in mean PAH SDS was observed, 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 at study entry, were restored to within the normal range with somatropin therapy.

The most frequently reported AEs were associated with both NutropinAq and placebo and were fever, infection, vomiting, cough increased, pharyngitis, rhinitis and otitis media. There was a high incidence of urinary tract infections.

Growth failure associated with Turner Syndrome

One pivotal, multicentre, open label, controlled study has been conducted in Turner Syndrome. Patients received an s.c. dose of 0.125 mg/kg three times a week or 0.054 mg/kg/day, both regimens giving a cumulative weekly dose of approximately 0.375 mg/kg. Patients under 11 years of age were also randomised to receive oestrogen therapy, either in late (aged 15 years) or early (aged 12 years) adolescence.

A total of 117 patients were treated with somatropin; 36 received somatropin 0.125 mg/kg three times a week and 81 patients received 0.054 mg/kg somatropin daily. The average treatment time was 4.7 years in the somatropin three times a week group and 4.6 years in the somatropin daily group.

Growth rate 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 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. Compared with matched historical controls, early somatropin therapy (mean duration of 5.6 years) combined with oestrogen replacement at age 12 years resulted in an adult height gain of 5.9 cm (n=26), whereas girls who initiated oestrogen at age 15 years (mean duration of somatropin therapy 6.1 years) had a mean adult height gain of 8.3 cm (n=29). Thus, the greatest improvement in adult height was observed in patients who received early GH treatment and oestrogen after age 14 years.

The most commonly reported AEs were flu syndrome, infection, headache, pharyngitis, rhinitis and otitis media. These events are expected in children and were mild/moderate AEs.

Growth hormone deficiency in adults

Two pivotal, multicentre, placebo-controlled, double-blind studies have been conducted in patients diagnosed with adult growth hormone deficiency (AGHD), one in adult-onset AGHD (n=166) and the other in childhood-onset AGHD (n=64). The dose of somatropin was 0.0125 mg/kg/day sc in adult-onset AGHD and 0.0125 or 0.025 mg/kg/day in childhood-onset AGHD.

In both studies, somatropin treatment resulted in significant changes 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, and at the 24-month time point in the childhood-onset study. At the 12-month time point, the percentage change was higher in the childhood-onset study than in the adult-onset study. No significant changes in bone mineral density (BMD) were observed in adult-onset AGHD patients, however in the childhood-onset study, all groups had an increase in BMD at 24 months, 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.

Supporting data from a study on adult-onset GHD patients were generally consistent with those of the pivotal studies, with some improvements in BMD.

The most frequently reported AEs in the two pivotal studies were headache, oedema, arthralgia/arthritis, tenosynovitis, paraesthesia and allergic reaction/rash. The incidence of these AEs was also high in the placebo groups.

5.2 Pharmacokinetic properties

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

General characteristics

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.

Biotransformation

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 $t_{1/2}$ of somatropin is about 2.3 hours. After intravenous bolus administration of somatropin, the mean terminal half-life $t_{1/2\beta}$ or $t_{1/2\gamma}$ 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.

Special populations

Information about the pharmacokinetics of somatropin in elderly and paediatric populations, in different races or genders and in patients with renal or hepatic impairment is incomplete.

Paediatric population

Available literature data suggests that somatropin clearances are similar in adults and children.

Older people

Limited published data suggest that the plasma clearance and average steady-state plasma concentration of somatropin may not be different between young and elderly patients.

Race

Reported values for half-lives for endogenous GH in normal adult black males are not different from observed values for normal adult white males. No data for other races are available.

Growth hormone deficiency

Clearance and mean terminal half-life $t_{1/2}$ of somatropin in adult and paediatric growth hormone deficient patients are similar to those observed in healthy subjects.

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.

Turner syndrome

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.

Hepatic impairment

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

Gender

No gender-specific pharmacokinetic studies have been done with NutropinAq. The available literature indicates that the pharmacokinetics of somatropin are similar in men and women.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for human based on conventional acute and repeated-dose toxicity studies.

Carcinogenic potential

Carcinogenicity and genotoxicity studies have not been conducted with Nutropin Aq. In genotoxicity studies with other recombinant growth hormone preparations, there was no evidence of gene mutation in bacterial reverse mutation assays, chromosomal damage in human lymphocyte and mouse bone marrow cells, gene conversion in yeast or unscheduled DNA synthesis in human carcinoma cells. In carcinogenicity studies testing biologically recombinant active growth hormone in rats and mice, no increase in the incidence of tumors was shown.

Toxicity to reproduction and development

No conventional reproduction studies were performed. Somatropin is known to be associated with inhibition of the 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). Long-term treatment of monkeys during pregnancy and lactation and of newborn animals until adolescence, sexual maturity and reproduction did not indicate substantial disturbances of fertility, pregnancy, delivery, nursing or development of progeny.

Environmental risk assessment (ERA)

Under the proposed indications, the use of somatropin is not expected to result in an unacceptable risk to the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Liquified Phenol
Polysorbate 20
Sodium Citrate Dihydrate
Citric Acid, Anhydrous
Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

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. NutropinAq is designed to withstand a nominal (one hour maximum) period of time outside of the refrigerator on a daily basis.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the blister in the outer carton

For in-use storage conditions of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml of solution in a cartridge (Type I glass) closed with a stopper (butyl rubber) and a seal (rubber).
Pack sizes of 1, 3 and 6 cartridges.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling

NutropinAq is supplied as a multi-dose solution. After removal from the refrigerator, if the solution is cloudy, the content must not be injected. Gently swirl. Do not shake vigorously as it could

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.

A cartridge that is in the pen should not be removed during injections.

7. MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse,
92100 Boulogne-Billancourt,
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/164/003
EU/1/00/164/004
EU/1/00/164/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 February 2001

Date of latest renewal: 16 February 2006

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Genentech Inc.
1 DNA Way
South San Francisco
CA 94080-4990
USA

Name and address of the manufacturer responsible for batch release

Ipsen Pharma Biotech SAS
Parc d'Activités du Plateau de Signes,
Chemin Départemental no 402,
83870 Signes
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Pharmacovigilance System**

The marketing authorisation holder (MAH) must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

• **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same

time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
CARTON - 1 CARTRIDGE**

1. NAME OF THE MEDICINAL PRODUCT

NutropinAq 10 mg/2 ml (30 IU), solution for injection
somatropin

2. STATEMENT OF ACTIVE SUBSTANCE

One ml contains 5 mg of somatropin
One cartridge contains 10 mg (30 IU) of somatropin

3. LIST OF EXCIPIENTS

Other ingredients: sodium chloride, liquefied phenol, polysorbate 20, sodium citrate dihydrate, citric acid anhydrous and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 cartridge containing 2 ml solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening, use before 28 days at 2°C – 8°C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the blister in the outer carton.

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma, 65 quai Georges Gorse, 92100 Boulogne-Billancourt, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/164/003 1 cartridge
EU/1/00/164/004 3 cartridges
EU/1/00/164/005 6 cartridges

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NutropinAq 10 mg/2 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
{CARTON - 3 CARTRIDGES}**

1. NAME OF THE MEDICINAL PRODUCT

NutropinAq 10 mg/2 ml (30 IU), solution for injection
somatropin

2. STATEMENT OF ACTIVE SUBSTANCE

One ml contains 5 mg of somatropin
One cartridge contains 10 mg (30 IU) of somatropin

3. LIST OF EXCIPIENTS

Other ingredients: sodium chloride, liquefied phenol, polysorbate 20, sodium citrate dihydrate, citric acid anhydrous and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

3 cartridges containing 2 ml solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening, use before 28 days at 2°C – 8°C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the blister in the outer carton.

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma, 65 quai Georges Gorse, 92100 Boulogne-Billancourt, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/164/003 1 cartridge

EU/1/00/164/004 3 cartridges

EU/1/00/164/005 6 cartridges

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

NutropinAq 10 mg/2 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
{CARTON - 6 CARTRIDGES}**

1. NAME OF THE MEDICINAL PRODUCT

NutropinAq 10 mg/2 ml (30 IU), solution for injection
somatropin

2. STATEMENT OF ACTIVE SUBSTANCE

One ml contains 5 mg of somatropin
One cartridge contains 10 mg (30 IU) of somatropin

3. LIST OF EXCIPIENTS

Other ingredients: sodium chloride, liquefied phenol, polysorbate 20, sodium citrate dihydrate, citric acid anhydrous and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

6 cartridges containing 2 ml solution for injection

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening, use before 28 days at 2°C – 8°C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the blister in the outer carton.

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.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma, 65 quai Georges Gorse, 92100 Boulogne-Billancourt, France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/164/003 1 cartridge
EU/1/00/164/004 3 cartridges
EU/1/00/164/005 6 cartridges

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NutropinAq 10 mg/2 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
{BLISTER}**

1. NAME OF THE MEDICINAL PRODUCT

NutropinAq 10 mg/2 ml (30 IU) solution for injection
somatropin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use.
Read the package leaflet before use. Store in a refrigerator.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
{CARTRIDGE}**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

NutropinAq 10 mg/2 ml
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NutropinAq 10 mg/2 ml (30 IU) solution for injection somatropin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NutropinAq is and what it is used for
2. What you need to know before you use NutropinAq
3. How to use NutropinAq
4. Possible side effects
5. How to store NutropinAq
6. Contents of the pack and other information

1. What NutropinAq is and what it is used for

NutropinAq contains somatropin which is a recombinant growth hormone similar to the human's natural growth hormone made by your body. It is recombinant, meaning it is made outside of the body by a special process. Growth Hormone (GH) is a chemical messenger made by a small gland in your brain called the pituitary. In children it tells the body to grow, help the bones to develop normally and, in later adult life, GH helps to maintain a normal body shape and metabolism.

In children, NutropinAq is used:

- When your body does not make enough growth hormone and for this reason you are not growing properly.
- When you have Turner syndrome. Turner syndrome is a genetic abnormality in girls (absence of female sexual chromosome(s)) that prevents growth.
- When your kidneys are damaged and they lose their ability to function normally with an impact on growth.

In adults NutropinAq is used for:

- If your body does not make enough growth hormone as an adult. This can start during adult life or continue from when you were a child.

Benefits if using this medicine

In children, it helps the body to grow and the bones to develop normally.

In adults, it helps to maintain normal body shape and metabolism for example lipid profile and glucose levels.

2. What you need to know before you use NutropinAq

Do not use NutropinAq:

- if you are allergic to somatropin or any of the other ingredients of this medicine (listed in section 6).
- in children if the bones have already stopped growing.
- if you have an active tumour (cancer). Tell your doctor if you have or have had an active tumour. Tumours must be inactive and you must have finished your anti-tumour treatment before you start treatment with NutropinAq.

- if you have complications after a major surgery (open-heart or abdominal surgery), a multiple trauma, acute respiratory failure, or similar conditions.

Warning and Precautions

Talk to your doctor or pharmacist before using NutropinAq.

- If you experience visual changes, bad or frequent headache, associated with feeling sick (nausea) or vomiting, especially at the start of treatment, tell your doctor immediately. These could be signs of a temporary increase in pressure within the brain (intracranial hypertension).
- If during growing, a limp or hip or knee pain develops, ask the doctor for advice.
- If you notice a curve of your spine (scoliosis) you will need to be checked often by your doctor as scoliosis may progress in any child during rapid growth.
- Your doctor should monitor you for high blood sugar levels (hyperglycemia) during treatment with NutropinAq. If you are treated with insulin, your doctor may need to adjust your insulin dose. If you have diabetes and associated severe/worsening eye disease you should not be treated with NutropinAq.
- Your doctor should check your thyroid function periodically and if necessary prescribe adequate treatment. If you have an underactive thyroid gland leading to low levels of thyroid hormone (hypothyroidism) it should be treated before you start NutropinAq treatment. If your hypothyroidism is not treated, it could stop NutropinAq from working.
- If you have a replacement therapy with glucocorticoids you should consult your doctor regularly as you may need adjustment of your glucocorticoid dose.
- If you have had a tumour (cancer) in the past, specially a tumour affecting the brain, your doctor should pay special attention and examine you regularly for a possible return of the tumour.
- A small number of growth hormones deficient patients treated with growth hormone have had leukaemia (blood cancer). However, no cause and effect relationship with growth hormone treatment has been proven.
- If you undergo a kidney transplant NutropinAq treatment should be stopped.
- If you have complications after major surgery (open-heart or abdominal surgery), multiple trauma, acute respiratory failure, or similar conditions, your doctor should decide whether it is safe to continue NutropinAq treatment.
- There may be an increased risk of developing an inflammation of the pancreas (pancreatitis), which causes severe pain in the abdomen and back. Contact your doctor if you or your child develops stomach ache after taking NutropinAq.
- If you have Prader-Willi syndrome, you should not be treated with NutropinAq unless you have growth hormone deficiency.

Other medicines and NutropinAq

Tell your doctor or pharmacist if you are using, have recently used or might take any other medicines.

- if you have a replacement therapy with glucocorticoids it may reduce the effect of NutropinAq on growth. You should consult your doctor regularly as you may need adjustment of your glucocorticoid dose.
- if you are treated with insulin, your doctor may need to adjust your insulin dose.
- if you are treated with sex steroids, anticonvulsants or cyclosporin ask the doctor for advice. If you are diagnosed with adrenal insufficiency during NutropinAq treatment, you require steroid treatment. If you are already treated for adrenal insufficiency you may require an adjustment of your steroid dose.
- in particular, inform your doctor if you are taking or have recently taken any of the following medicines. Your doctor may need to adjust the dose of NutropinAq or of the other medicines:

- Oestrogen taken orally or other sex hormones

Pregnancy and breast-feeding

You should stop taking NutropinAq if you are pregnant.

Caution should be exercised while breast-feeding during treatment with NutropinAq.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

No effect on ability to drive or use machines has been noticed while using NutropinAq.

NutropinAq is essentially “sodium free”

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium-free”.

3. How to use NutropinAq

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. NutropinAq therapy should be carried out under regular guidance of a doctor who is experienced in growth hormone deficiency.

The dose of NutropinAq to be injected will be decided by your doctor. Do not change the dosage without consulting your doctor. The recommended dose is:

In children with growth hormone deficiency:

0.025 - 0.035 mg/kg bodyweight injected each day under the skin (subcutaneous injection).

In girls with Turner syndrome:

Up to 0.05 mg/kg bodyweight injected each day under the skin (subcutaneous injection).

In children with chronic renal insufficiency:

Up to 0.05 mg/kg bodyweight injected each day under the skin (subcutaneous injection). You can continue treatment with NutropinAq until you have a kidney transplant.

In adults with growth hormone deficiency:

Low initial doses of 0.15 - 0.3 mg injected each day under the skin (subcutaneous injection). Then the doctor can increase the dose depending on your response. The final dose is rarely above 1.0 mg/day. In general, the lowest dose leading to a response should be given to you.

Treatment with NutropinAq is a long-term therapy. For further information ask your doctor.

How to inject NutropinAq

The dose of NutropinAq to be injected will be decided by your doctor. You have to inject NutropinAq every day under the skin (subcutaneous injection). It is important to change the place where you have your injection every day to avoid damaging your skin.

NutropinAq is supplied as a multi-dose solution. After removal from the refrigerator, if the solution is cloudy, the content must not be injected. Gently swirl. Do not shake vigorously as it could denature the protein.

To inject NutropinAq you should use the NutropinAq Pen. For each injection you should use a new sterile injection needle. Read all the instructions for use carefully (on the reverse) before you start using NutropinAq Pen. At the start of therapy, it is recommended that a doctor or a nurse give you the injection and train you with the NutropinAq Pen. After this training, you will be able to inject yourself or be injected by a trained care-giver.

If you use more NutropinAq than you should

If you have injected more NutropinAq than you should have, contact your doctor for advice. If you inject too much NutropinAq, your blood sugar level may decrease and become too low and then rise too high (hyperglycaemia).

If you inject too much NutropinAq over a long period of time (years), you may experience some overgrowth of parts of your body such as ears, nose, lips, tongue and cheekbone (gigantism and/or acromegaly).

If you forget to take NutropinAq

Do not take a double dose to make up for a missed dose. Continue with your usual dosage the next day and tell your doctor at your next appointment.

If you stop using NutropinAq

Ask advice from you doctor before you stop using NutropinAq. If you stop using NutropinAq too early or for too long, the results will not be as expected.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you notice any change or increase in growth of birthmarks and/or moles (melanocytic naevus). In case of a tumour or re-growth of previous tumours (confirmed by your doctor), treatment with NutropinAq must be stopped immediately. This side effect is uncommon, it may affect up to 1 in 100 patients.

Tell your doctor immediately if you experience visual changes, bad or frequent headaches, associated with feeling sick (nausea) or vomiting. These could be symptoms of a temporary increase in pressure within the brain (intracranial hypertension). If you have intracranial hypertension, your doctor may decide to temporarily reduce or discontinue NutropinAq therapy. Then therapy may be started again after the episode is over. This side effect is rare, it may affect up to 1 in 1,000 patients.

Other side effects include:

Very common (may affect more than 1 in 10 patients)

Swelling of the hands and feet due to an accumulation of fluid (peripheral oedema) sometimes associated with localised muscle pain (myalgia) and pain in joints-(arthralgia). These side effects appear usually in adults early in treatment and are short-lived. Oedema was reported as common in children.

Common (may affect up to 1 in 10 people)

Underactivity of the thyroid gland leading to low levels of thyroid hormone (hypothyroidism). If your hypothyroidism is not treated, it could stop NutropinAq from working. Your doctor should check your thyroid function periodically and if necessary prescribe adequate treatment.

Reduced ability to absorb sugar (glucose) from your blood leading to high blood sugar levels (hyperglycemia). Your doctor should monitor you for signs of this during treatment with NutropinAq. If you are treated with insulin, your doctor may need to adjust your insulin dose.

Feeling of weakness (asthenia) and increased muscle tension (hypertonia)

Pain, bleeding, bruising, rash and itching at the site of injection. These can be avoided by using the correct injection technique and changing the sites of injection.

Some patients may develop antibodies (a type of protein produced by the body) to somatropin. When these antibodies were found in patients, it did not prevent them from growing.

Uncommon (may affect up to 1 in 100 people)

Decrease in the number of red blood cells in the blood (anaemia), decrease in blood sugar level (hypoglycaemia) and increase in phosphate levels (hyperphosphatemia).

Personality changes or abnormal behaviour.

Persistent stinging, burning sensation, pain and/or numbness in the palm of the hand due to a trapped nerve at the wrist (carpal tunnel syndrome).

Rapid involuntary movements of the eyes (nystagmus), swelling of the optic nerve in the eye (papilloedema), double vision (diplopia), headache, somnolence and vertigo.

Increased heart rate (tachycardia) and high blood pressure (hypertension). Vomiting, stomach pain, wind (flatulence) and feeling of sickness (nausea).

Sensitive and dry skin (exfoliative dermatitis), changes in thickness of the skin, excessive growth of hair on the face and body (hirsutism), hives (urticaria).

Curvature of the spine (scoliosis). If you have scoliosis, you will need to be frequently checked for an increase in the curve.

Bone disorder where the upper leg (femur) moves apart from the hip (slipped capital femoral epiphysis). This happens generally in patients who grow rapidly. Patients with endocrinological disorders are more prone to develop a slipped capital femoral epiphysis.

Decrease in muscle size (muscle atrophy), joint pain (arthralgia) and bone pain.

Difficulty to hold-in urine (urinary incontinence), high frequency (pollakiuria) and volume (polyuria) of urination.

Bleeding from the womb (uterine haemorrhage), genital discharge and breast enlargement (gynaecomastia).

Localised loss/gain of fat from the skin (lipodystrophy, injection site atrophy/hypertrophy)
Enlarged adenoids with similar symptoms as enlarged tonsils (see rare).

Rare (may affect up to 1 in 1,000 people)

Increase in blood sugar levels (hyperglycaemia, diabetes mellitus). Diabetes mellitus can lead to increased urination, thirst and hunger. If you experience any of these symptoms, you should inform your doctor.

Enlarged tonsils leading to snoring, difficulty breathing or swallowing, brief interruption of breathing during sleep (sleep apnea), or fluid in the ear, as well as infections of the ear. If this appears to be particularly troublesome, you should discuss it with your doctor.

Abnormal sensations of tingling, pricking or numbness (paraesthesia), abnormal bone development, disease affecting progress of bone growth (osteochondrosis) and muscle weakness.

Other rare side effects seen with NutropinAq treatment include itching over the whole body, rash, blurred vision, increased weight, dizziness, diarrhoea, swelling of the face, fatigue, pain, fever,

depression and difficulty to sleep (insomnia).

Indication specific side effects seen during clinical trials

In children with growth hormone deficiency brain (central nervous system) tumours were commonly reported. From the 236 patients enrolled into the clinical studies 3 patients had a central nervous system tumour. Of the 3 patients with a central nervous system tumour, 2 patients experienced a recurrent medulloblastoma and 1 patient experienced a histiocytoma. See also section “warning and precautions”.

Girls with Turner syndrome commonly reported abnormally heavy bleeding at menstruation.

Children with chronic renal insufficiency commonly reported inflammation of the lining of the abdomen (peritonitis), bone necrosis and an increase of creatinine blood levels. They are more likely to develop increased pressure in the brain (intracranial hypertension), with the greatest risk at the beginning of treatment, although children with organic growth hormone deficiency and Turner syndrome also have an increased incidence.

Adults with growth hormone deficiency commonly reported abnormal sensations of tingling, pricking or numbness (paraesthesia), abnormally high levels of blood glucose, excess of lipids (fat) in the blood, sleeplessness, joint disorders, arthrosis (degenerative joint disease), muscle weakness, back pain, breast pain and breast enlargement (gynaecomastia).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store NutropinAq

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label of the cartridge and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the blister in the outer carton.

After first use, the cartridge may be stored for up to 28 days at 2°C - 8°C. Do not remove the cartridge that is being used from the NutropinAq Pen between injections.

Do not use NutropinAq if you notice that the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Content of the pack and other information

What NutropinAq contains

The active substance of NutropinAq is somatropin*.

* Somatropin is a human growth hormone produced in *Escherichia coli* cells by recombinant DNA technology.

The other ingredients are sodium chloride, liquefied phenol, polysorbate 20, sodium citrate dihydrate,

citric acid anhydrous and water for injections.

What NutropinAq looks like and contents of the pack

NutropinAq is a solution for injection (in a cartridge (10 mg/2 ml) - pack size of 1, 3 and 6). The solution for multidose use is clear and colourless.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Ipsen Pharma, 65 quai Georges Gorse, 92100 Boulogne-Billancourt, France

Manufacturer : IPSEN PHARMA BIOTECH S.A.S., Parc d'Activités du Plateau de Signes, CD no 402, 83870 Signes, France

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

NutropinAq Pen Instruction for use with NutropinAq

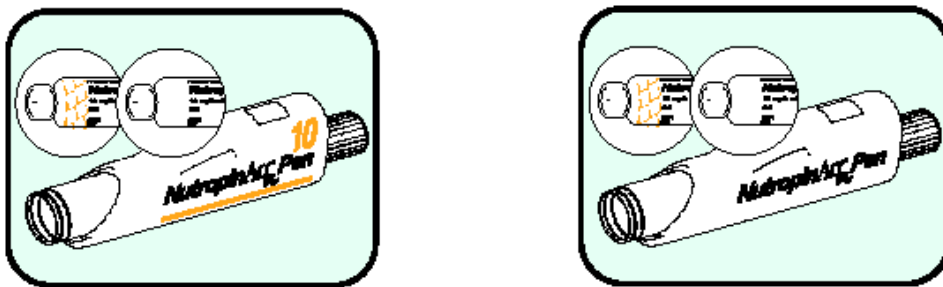
DO NOT INJECT THE MEDICINE UNTIL YOUR DOCTOR OR NURSE HAS THOROUGHLY TRAINED YOU IN THE PROPER TECHNIQUES.

Caution:

Before using your NutropinAq Pen, please read the following instructions carefully. We also suggest you consult your doctor or nurse for a demonstration.

The NutropinAq Pen is designed for use only with cartridges of NutropinAq (for subcutaneous use only).

As shown by the illustrations below, NutropinAq pen and cartridges are available in two designs (with or without additional yellow colour). The working of the pen and the content of the cartridges are the same for both designs. Either of the NutropinAq cartridge designs can be used with either of the NutropinAq Pen designs.



Only use the pen needles recommended by your doctor or nurse.

The dosage scale located beside the window of the cartridge holder should not be used as a dose measurement. It should only be used to estimate the dosage remaining in the cartridge. Always refer to the LCD (Liquid Crystal Display), not audible clicks, for setting an injection of NutropinAq. The clicks are only audible confirmation that the black dose knob has been moved.

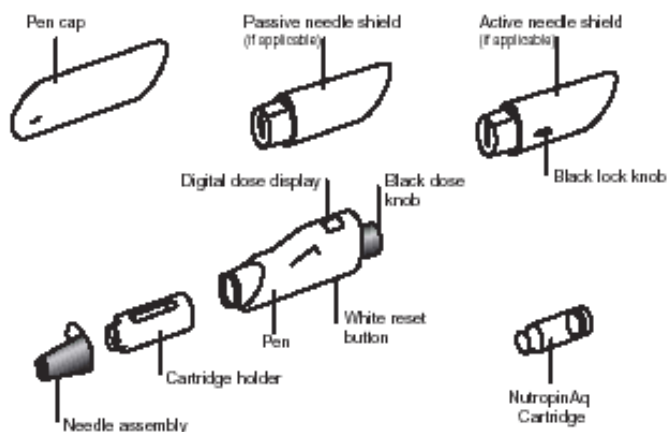
Always store the pen and cartridges in a clean, safe place in the refrigerator at a temperature between 2-8°C and out of children's reach and sight. Protect from intense light. Use a cooler to store your NutropinAq Pen when travelling. The NutropinAq is designed to withstand a nominal (one hour maximum) period of time outside of the refrigerator on a daily basis. Avoid areas of extreme temperature. Check the expiry date of the cartridge before use.

To guard against the spread of infection, follow these safety measures:

- Wash your hands thoroughly with soap and water before using your pen.
- Clean the cartridge rubber seal with an alcohol swab or cotton ball saturated with alcohol.
- Avoid touching the cartridge rubber seal at all times.
- If you accidentally touch the cartridge rubber seal, clean it with an alcohol swab.
- Do not use the same needle for more than one person.
- Use needles only once.

NutropinAq Pen Components:

Shown below are the items necessary for giving an injection. Gather all of these components prior to use.

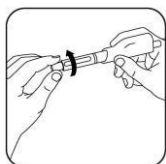


Your NutropinAq cartridge and Pen will be supplied separately.

Part I: Preparing and Injecting

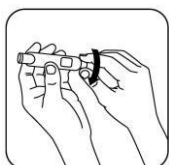
Follow the instructions in this section if you are using the pen for the first time or are replacing an empty cartridge.

Inspect all new cartridges prior to use. Occasionally, after refrigeration, you may notice that small colourless particles are present in the NutropinAq solution. This is not unusual for solutions containing proteins like NutropinAq and does not affect the strength of the product. Allow the cartridge to come to room temperature and gently swirl. Do not shake. If the solution is cloudy or hazy or contains any solid matter, the cartridge should not be used. Return the cartridge to your pharmacist or prescribing doctor.

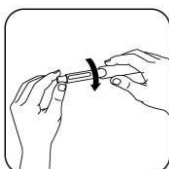


1. Remove the green pen cap and unscrew the cartridge holder from the pen. If necessary, remove the empty cartridge and discard it properly.

2. Press the white reset button.



3. Turn the black dose knob counter-clockwise back to its starting position until it no longer turns. (*See illustration.*) Then turn the dose knob clockwise until the first click position is reached (approximately $\frac{1}{4}$ turn). This ensures that the plunger push rod is reset to the starting position. If this is not done when the dosage knob is first pushed in, NutropinAq will be wasted or the cartridge may crack.



4. Insert cartridge into the cartridge holder, then screw the cartridge holder back onto the pen. (*Be careful not to touch the rubber seal.*)

5. Remove the paper seal from a new needle assembly and screw it onto the cartridge holder.

6. Carefully remove both protective caps from the needle by pulling gently. Do not throw the larger cap away as it will be used later for proper needle removal and disposal.



7. Holding the pen with the needle pointing upward, gently tap the cartridge holder to move any air bubbles to the top. While still holding the pen in the upright

position, push in the black dose knob until it clicks into position. You should see a drop of solution appear.

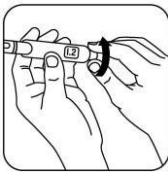
Be patient. If the medicine does not appear within a few seconds, you may need to push the reset button again.



8. If no drop of medicine appears, push the white reset button again. Now turn the black dose knob clockwise (*See illustration*) by one click (0.1mg). If you accidentally turn it too far, go back one click (0.1 mg).

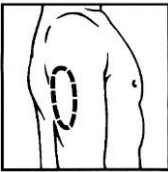
9. While still holding the pen in the upright position, push in the black dose knob again and watch the needle tip for a drop of medicine to appear. Repeat steps 8 and 9 until it appears.

10. Press the white reset button.

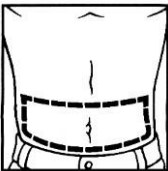


11. Set the required dose by turning the black dose knob. If you cannot dial the full dose, either start a new cartridge (as described in Part I), or inject the partial dose. Then, start a new cartridge (as described in Part I) to administer the remaining portion of your medication. Your doctor or nurse will advise you on the procedure for administering the last dose in the cartridge.

Prepare the injection site by wiping with an antiseptic impregnated swab. Injection sites include the upper arms, abdomen, and upper thighs. Change the injection sites to avoid discomfort. Even if you develop a preference for one site, you still should rotate the injection site.



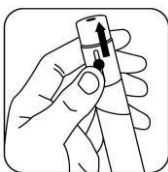
Upper Arm



Abdomen



Thigh



12. If you are using the passive shield (or no shield) proceed to step 13. If you are using the active shield, slide the shield onto the pen and push the 2 black lock knobs on the needle shield toward the tip.

13. Set the tip of the pen on the prepared injection site and press the needle into the skin by pushing the pen downward until the shield is totally depressed. Your doctor or nurse will show you how to do this. Now you are ready to administer the dose. Press down on the black dose knob. Keeping pushed the dose button for 5 seconds after expelling the dose, then withdraw the pen from the skin. A drop of

blood may appear. Put a plaster on the injection site if you wish.

14. Pull the needle shield off the pen (if you have used one) and place the larger needle cap on a flat surface. Slide the needle in to pick it up and push the cap completely down over the needle. Twist off the needle and discard it properly. Your doctor or nurse will tell you how to dispose of the items you have used for the injection. Always store your disposal container out of the reach of children.

15. Attach the pen cap and return it to its case with the black dose knob pressed in. You should always store the pen in a refrigerator. Do not remove cartridge between injections. **DO NOT FREEZE.**

For subsequent injections with the NutropinAq Pen, attach a new needle, push the white reset button and dial your dose.

Part II: Storage and Maintenance

Follow these tips to ensure proper care of your NutropinAq Pen:

- Always keep your NutropinAq Pen and cartridge refrigerated and protected from light when not in use.
- You may remove the pen and cartridge from the refrigerator up to 45 minutes prior to use.
- Do not let your NutropinAq Pen and/or cartridge freeze. Contact your doctor or nurse for a replacement if either the pen or cartridge does not work.
- Avoid excessive temperatures. The solution in the cartridge is stable for up to 28 days after first use when stored at 2 - 8°C.
- If your pen requires cleaning, do not place under water. Use a damp cloth to wipe away dirt. Do not use alcohol.
- When priming a new cartridge, you may need to repeat Part I, steps 8 and 9 up to a total of 6 times (0.6 mg) to remove air bubbles. Small bubbles may remain and will not affect the dose.
- The pen should contain the NutropinAq that is being used. Do not remove cartridge between injections.
- The NutropinAq cartridge may be used for up to 28 days.
- Do not store the NutropinAq Pen with needle attached.
- Avoid the use of the pen adjacent to or stacked with other equipment because it could result in increased electromagnetic emissions or decreased electromagnetic immunity and results in improper performance of the pen.

In addition, Portable Radio Frequency communications equipment should be used no closer than 30 cm (12 inches) to any part of the pen. Otherwise, it could lead to a degradation of the performance of the pen.

Part III: Needles for the NutropinAq Pen

Your doctor or nurse will recommend a needle that is appropriate for you. Always use the needles recommended.

Needles from other countries may not fit on your NutropinAq Pen. If you travel outside the European Union, make sure you take enough needles for the duration of your stay.

Part IV: Commonly Asked Questions

Q: Do I need to change the needle every time I use my NutropinAq Pen?

A: Yes. A new needle should be used for every injection. The needle is only sterile on the first use.

Q: Where should I store my NutropinAq Pen?

A: Your NutropinAq Pen should be stored in the case, inside a refrigerator when a cartridge is inserted. When travelling, place your pen case in a cooler. **DO NOT FREEZE.**

Q: Why do I keep my medication in the refrigerator?

A: To maintain its strength.

Q: Can I store my NutropinAq Pen in the freezer?

A: No. Freezing will damage the pen and medicine.

Q: How long can I keep my NutropinAq Pen and cartridge outside the refrigerator?

A: We recommend no longer than one hour. Your doctor or nurse will advise you regarding pen storage.

Q: What is the maximum dose the NutropinAq Pen can deliver in one injection?

A: The NutropinAq Pen can give a minimum dose of 0.1 mg up to a maximum dose of 4.0 mg (40 clicks). If you attempt to dose more than 4 mg at a time, the medicine will either be forced out of the needle and wasted or excess pressure will be placed upon the cartridge and it may crack.

Q: Is it possible to turn the black dose knob back if I click too many times?

A: Yes. You can turn the black dose knob backwards until the correct number appears in the LCD.

Q: What should I do if there is not enough solution left in the cartridge for my next dose?

A: Your doctor or nurse will advise you what to do for the last dose in the cartridge.

Q: Why do I have to rewind the black dose knob on my NutropinAq Pen every time I replace the cartridge?

A: This ensures that the plunger push rod completely resets itself back to the starting position. If this is not done, liquid will come out of the needle when a new cartridge is placed into the pen.

Q: Can I use my NutropinAq Pen without the shields?

A: Yes. Your NutropinAq Pen works without shields. The shields are optional to help you administer your injection.

Q: What should I do if I drop my NutropinAq Pen?

A: If you drop the NutropinAq Pen, check to see if the cartridge is damaged. You should also check the pen to see that the black dose knob is moving up and down properly and that the LCD counter is working. If your cartridge or pen is damaged, ask your doctor or nurse for a replacement.

Q: How long can I use my NutropinAq Pen?

A: The NutropinAq Pen is designed to last 24 months from the time you first use your pen.

Q: What does a blinking “bt” mean in the LCD?

A: The battery in your NutropinAq Pen is losing its charge. Please contact your doctor or nurse for a replacement pen. Batteries typically last 24 months and have a 4-week life from the time the „bt” first starts blinking.

Q: What does a blinking “[≡]” mean in the LCD ?

A: First warning of End of life : upon start up the flashing “end of life” warning signal indicates the coming termination of the pens lifetime. The “end of life” warning signal is displayed instead of the last dose. The pen will work for approximately one more month before the display will be permanently shut off.

Q: How do I replace my NutropinAq Pen?

A: Contact your doctor or nurse if you need a replacement part or if you need to replace your entire pen.

For more information, please contact the local representative. Your local representative and the manufacturer for the NutropinAq Pen device are the same as for the medicinal product detailed overleaf. Please see section 6 overleaf for contact details.

Manufacturer: IPSEN PHARMA BIOTECH S.A.S., Parc d’Activités du Plateau de Signes, CD no

402, 83870 Signes, France

This leaflet was last approved in <{MM/YYYY}>

CE 0459

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