NUTROPINAQ 10 mg / 2 ml (30 IU), solution for injection
1 glass cartridge of 2 ml (CIP: 364 062-2)

Applicant: IPSEN PHARMA

somatropin
ATC code: H01AC01

List I
Initial annual hospital prescription reserved for specialists in paediatrics and/or endocrinology and metabolic disorders practicing in specialist paediatric and/or endocrinology and metabolic disorders departments.

Date of initial Marketing Authorisation: 16 February 2001 (centralised procedure)

Reason for request: Re-assessment of the actual benefit (AB) in accordance with Article R 163-21 of the social security code for children with no deficiency:
- Growth failure associated with Turner syndrome.
- Growth failure associated with chronic renal insufficiency.

This re-assessment does not relate to the indications involving children who are deficient in growth hormone.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. **Active ingredient**
Somatropin

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

1.3. **Dosage**

Table 1: NUTROPIINAQ dosage in indications in non-deficient children

<table>
<thead>
<tr>
<th>Indication</th>
<th>mg/kg of body weight dose per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner syndrome</td>
<td>Up to 0.050</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Up to 0.050</td>
</tr>
</tbody>
</table>
Table 2: AB of proprietary growth hormone products in the indications in non-deficient children

<table>
<thead>
<tr>
<th>Proprietary products</th>
<th>Turner syndrome</th>
<th>Renal disease in pre-pubescent children</th>
<th>Renal disease in pubescent children</th>
<th>Prader-Willi syndrome</th>
<th>SHOX deficiency</th>
<th>Growth failure in children born small for gestational age or with intrauterine growth restriction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotonorm</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Moderate</td>
<td>-</td>
<td>Moderate</td>
</tr>
<tr>
<td>Norditropin</td>
<td>Substantial</td>
<td>Substantial</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nutropinaq</td>
<td>Substantial</td>
<td>Substantial</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Saizen</td>
<td>Substantial</td>
<td>Substantial</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Moderate</td>
</tr>
<tr>
<td>Humatrope</td>
<td>Substantial</td>
<td>Substantial</td>
<td>-</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Zomacton</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Moderate</td>
<td>-</td>
<td>Moderate</td>
</tr>
<tr>
<td>Omnitrope</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*The Transparency committee has limited the scope of the AB to a height of < -3 SD even though the Marketing Authorisation relates to heights of < -2.5 SD.

Table 3: Level of the IAB of proprietary growth hormone products in the indications in non-deficient children

<table>
<thead>
<tr>
<th>IACB date obtained</th>
<th>Turner syndrome</th>
<th>Renal disease in pre-pubescent children</th>
<th>Renal disease in pubescent children</th>
<th>Prader-Willi syndrome</th>
<th>SHOX deficiency</th>
<th>Growth failure in children born small for gestational age or with intrauterine growth restriction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norditropin</td>
<td>II (Sept 1996)</td>
<td>II (Sept 1996)</td>
<td>-</td>
<td>-</td>
<td>V</td>
<td>V (Jul 2004)</td>
</tr>
<tr>
<td>Nutropinaq</td>
<td>V (Sept 2004)</td>
<td>V (Sept 2004)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Humatrope</td>
<td>II (Oct 1996)</td>
<td>II (May 2000)</td>
<td>-</td>
<td>IV</td>
<td>V</td>
<td>V (Jul 2007)</td>
</tr>
<tr>
<td>Zomacton</td>
<td>V (Oct 2001)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Omnitrope</td>
<td>V (Jan 2007)</td>
<td>V (Jan 2007)</td>
<td>V (Jan 2007)</td>
<td>-</td>
<td>V</td>
<td>V (Jan 2007)</td>
</tr>
</tbody>
</table>
3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2011)

H: Systemic hormones, excluding sex hormones
H01: Pituitary and hypothalamic hormones and analogues
H01A: Adenohypophyseal hormones and analogues
H01AC: Somatropin and analogues
H01AC01: Somatropin

3.2. Medicines in the same therapeutic category

Table 4: Indications for proprietary medicinal products containing growth hormone in children

<table>
<thead>
<tr>
<th>Growth hormone deficiency</th>
<th>Turner syndrome</th>
<th>Renal disease in pre-pubescent children</th>
<th>Renal disease in pubescent children</th>
<th>Prader-Willi syndrome</th>
<th>SHOX deficiency</th>
<th>Growth failure in children born small for gestational age or with intrauterine growth restriction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotonorm</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Nutropinaq</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Saizen</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Humatrope</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Zomacton</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Omnitrope</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
<td>+</td>
</tr>
</tbody>
</table>

4 DRUG USE DATA

These proprietary medicinal products are not prescribed often enough to appear in the prescription panels available to us (IMS and GERS).

Usage data are available for the indications: Turner syndrome and chronic renal insufficiency.

Turner syndrome and chronic renal disease

In these two indications, the only data on use available, from a CNAMTS study published in 2004, are as follows:

- **Turner syndrome**: Almost 900 patients treated (estimate for the whole of France), mean age 12.5 years, severe associated disorders (mainly cardiac or pulmonary malformation) in 9% of cases, criteria for starting treatment (bone age < 12 years according to the SPC) not respected in 6% of cases, mean duration of treatment 5.6 years, mean total increase in height + 2.35 SD with respect to the Turner growth charts and + 1.06 SD with respect to the reference growth charts, criteria for discontinuation of treatment (according to the SPC) not respected in 13% of patients (increase in height in the last year of treatment, bone and height age), dosages between 0.7 and 0.9 IU/kg/week in 77% of cases (more than 0.9 IU/kg/week in 15% of patients treated) most frequent
reasons for discontinuation: bone age limit passed, inadequate treatment response, decision of the patient of his/her family.

- *Chronic renal disease* (only for the indication “prepubescent children”): About 220 patients treated (estimate for the whole of France), mean age 11.1 years, severe associated disorders (disorder caused by or associated with CRD) in 28% of cases, criteria for starting treatment (height, age, bone age, signs of puberty) defined by the SPC not respected in 60% of cases, mean duration of treatment 4 years, mean total increase in height + 1.1 SD over the mean duration of treatment, criteria for discontinuation of treatment in the SPC not respected in 18.5% of patients (increase in height in the last year of treatment, bone and height age), mean dosage 1.04 IU/kg/week, most frequent reasons for discontinuation: mainly logical consequence of kidney transplantation.

Finally, no post-registration studies requested by HAS are underway for these two indications, the requests formulated by the authorities in 2000 were withdrawn in 2002 at the request of the manufacturer concerned.

5 DATA ON TREATMENT PROCEDURES WITH GROWTH HORMONE IN EUROPE

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1 The authors note that it is possible that, in the context of chronic renal disease, the appearance of a break in the growth curve could lead the clinician to start treatment early because the course appears inevitable. This view was confirmed by work group conducting this assessment.
Table 5, below, details the European countries in which each of the propriety medicinal products on the market in France is refundable (in which indications, and at what level) together with special conditions of the availability of reimbursement. According to this information, it appears that:

- All European counties provide growth hormone treatment for Turner syndrome and renal disease.
- The indications SHOX, SGA and Prader-Willi syndrome are not treated in all countries.
- If they are treated, the whole cost of treatment is covered.
<table>
<thead>
<tr>
<th></th>
<th>Turner syndrome</th>
<th>Renal disease</th>
<th>Prader-Willi syndrome</th>
<th>SHOX deficiency</th>
<th>SGA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>if H &lt; -2 SDS</td>
</tr>
<tr>
<td>Denmark</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td>Prescribers limited to university specialists</td>
</tr>
<tr>
<td>Spain</td>
<td>100% if H &lt; -2 SDS age ≥ 2 years</td>
<td>100% if H &lt; -2 SDS age ≥ 2 years</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>if H &lt; -2.5 SDS and GR = 0</td>
</tr>
<tr>
<td>Estonia</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>Limited to children whose growth has not stopped</td>
</tr>
<tr>
<td>Finland</td>
<td>42%</td>
<td>100%</td>
<td>42%</td>
<td>0</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>100% if age ≥ 2 years</td>
<td>100% if age ≥ 2 years</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>No check of compliance with indications</td>
</tr>
<tr>
<td>Italy</td>
<td>100%</td>
<td>100%</td>
<td>100% if: 1/deficient, 2/ age prepubescent, 3/ IMC&lt;25, 4/ respiratory function normal</td>
<td>0</td>
<td>100%</td>
<td>Refundable for 2 years, extended on the advice of a regional committee</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Malta</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td>0</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Norway</td>
<td>Refundable from case to case</td>
<td>Refundable from case to case</td>
<td>If deficient</td>
<td></td>
<td></td>
<td>36%, with a ceiling of 56 Euros/T</td>
</tr>
<tr>
<td>Netherlands</td>
<td>100% if: H &lt; -1.5 SDS age ≥ 6 years</td>
<td>100% if: 1/H &lt; -1.3 SDS of parental height 2/Reduction in GR ≥ 0.25 SDS/year</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>Assessment of each patient’s file by a committee</td>
</tr>
<tr>
<td>Czech R.</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Slovakia</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>Indications refundable not defined, a single prescription point in the country</td>
</tr>
</tbody>
</table>
In 2007, during the reassessment of some proprietary growth hormone products in the indication “growth failure in children born small for gestational age who failed to show catch-up growth by the age of 4 years or later”, the Transparency Committee considered the demonstration of the benefit of this treatment in terms of the improvement in final height and the uncertainties relating to long-term tolerance of such treatment. The commission also considered the fact that small stature may not, of itself constitutes, a medical condition.

The reassessment was based on the data contained in the HAS report “L'hormone de croissance chez l’enfant non déficitaire” [Growth hormone in non-deficient children] (available under [http://www.has-sante.fr](http://www.has-sante.fr)) and the opinion of an expert from outside the working group. The HAS report was compiled on the basis of:
- all the literature data published up to May 2010,
- a meta-analysis of the clinical studies into the efficacy in respect of height, sponsored by HAS,
- the data supplied by the pharmaceutical companies,
- the opinion of a multidisciplinary working group,
- the recent results of a French tolerance study (SAGHE)\(^2\)
- the observations, recorded as appropriate, made in the course of the hearing by patients’ associations and healthcare professionals concerned with these rare conditions.

In addition, the HAS report evaluated the use of growth hormone from other viewpoints: psychological, social, medico-economic, regulatory and ethical.

6.1. Efficacy of growth hormone in non-deficient children

HAS commissioned a meta-analysis, indication by indication, that included clinical studies without limit of date of publication and covering all height criteria. Moreover, HAS carried out a bibliographical search that brought together all the observational studies. In addition, some unpublished data were supplied by the pharmaceutical companies. Details of the implementation of the meta-analysis and the references of all studies are presented in the HAS report “L'hormone de croissance chez l’enfant non déficitaire” [Growth hormone in non-deficient children] (available under [http://www.has-sante.fr](http://www.has-sante.fr)).

6.1.1. Turner syndrome

Meta-analysis of clinical studies

In Turner syndrome, the meta-analysis commissioned by HAS identified 11 randomised studies, with 12 comparisons and a total of 781 patients. The comparisons carried out were:
- growth hormone (GH) versus untreated,
- GH versus placebo,
- a “fixed dose” versus an “increasing dose” scheme,
- “3 injections per week” versus “6 injections per week”,
- “1 injection per day” versus “2 injections per day”,
- “increasing dose” versus “fixed dose”.

The mean population was 65 patients per group (between 9 and 78 per group). The first study was published in 1989, the last in 2007. Only one study was double blind, and 11 were open. All the studies included were reported in English. In addition to the studies included, 33

\(^2\) In November 2010, the results of the study “Santé Adulte GH Enfant” (SAGHE; Adult health following childhood GH) to evaluate the long-term mortality and morbidity of children exposed to growth hormone were presented. This relates to unpublished data made public by Afssaps in the form of an oral communication following a press conference organised by Afssaps in December 2010, an assessment of the risk/benefit ratio conducted by the EMA, the initial results of which were made public in May 2011, and the reassessment carried out by the FDA that was made public in April 2011.
studies were excluded. No unpublished studies were identified. No studies that were in progress at the time were identified by checking the registers and other sources. The study data that were included related to the following criteria:

- change of height SDS (6 studies),
- growth rate (1 year) (5 studies),
- final height (cm) (4 studies),
- final height SDS (3 studies),
- change of height (cm) (3 studies),
- height at the end of the study (cm) (2 studies),
- change of growth rate SDS (2 studies),
- growth rate SDS (2 studies),
- height at the end of the study SDS (2 studies),
- change of growth rate (cm/year) (1 study).

In the GH versus untreated comparison, GH was better than untreated in respect of:

- final height SDS: WMD\(^3\) = 1.15, 95% CI between 0.73 and 1.57, p < 0.0001, 1 study,
- final height (cm): WMD = 6.50, 95% CI between 4.28 and 8.72, p < 0.0001, 1 study,
- height at end of study (cm): WMD = 6.85, 95% CI between 5.00 and 8.69, p < 0.0001, 2 studies,
- height at end of study SDS: WMD = 1.82, 95% CI between 1.30 and 2.34, p < 0.0001, 1 study,
- change of height (cm): WMD = 7.34, 95% CI between 6.00 and 8.68, p < 0.0001, 2 studies,
- change of height SDS: WMD = 1.41, 95% CI between 1.26 and 1.57, p < 0.0001, 2 studies,
- growth rate (1 year): WMD = 3.11, 95% CI between 2.48 and 3.73, p < 0.0001, 2 studies,
- growth rate SDS: WMD = 3.20, 95% CI between 2.47 and 3.93, p < 0.0001, 1 study.

In the GH versus placebo comparison, GH is better than placebo in terms of growth rate (1 year): WMD = 2.60, 95% CI between 2.14 and 3.06, p < 0.0001, 1 study.

In the “fixed dose” versus “increasing dose” comparison, no significant difference in the height SDS criterion was detected at the end of the study (WMD = 0.16, 95% CI between -0.19 and 0.51, p = 0.3698, 1 study).

However, “fixed dose” is better than “increasing dose” in terms of:

- growth rate (1 year): WMD = 1.26, 95% CI between 0.80 and 1.72, p < 0.0001, 1 study,
- growth rate SDS: WMD = 1.09, 95% CI between 0.61 and 1.57, p < 0.0001, 1 study.

In the “3 injections per week” versus “6 injections per week”, “3 injections per week” comparison is worse than “6 injections per week” in terms of:

- change of height (cm): WMD = -2.70, 95% CI between -4.66 and -0.74, p = 0.0069, 1 study and,
- change of height SDS: WMD = -0.30, 95% CI between -0.52 and -0.08, p = 0.0082, 1 study.

In the “1 injection/day” versus “2 injections per day” comparison, no statistically significant difference between “1 injection/day” and “2 injections per day” was detected in terms of:

- final height (cm): WMD = -2.20, 95% CI between -7.06 and 2.66, p = 0.3746, 1 study,
- change of height SDS: WMD = 0.30, 95% CI between -0.24 and 0.84, p = 0.2765, 1 study,
- growth rate (1 year): WMD = 0.80, 95% CI between -0.15 and 1.75, p = 0.0979, 1 study,
- change of growth rate (cm/year): WMD = 0.80, 95% CI between -0.13 and 1.73, p = 0.091, 1 study.

In the “increasing dose” versus “fixed dose” comparison, “increasing dose” is better than “fixed dose” in terms of:

- final height SDS: WMD = 0.95, 95% CI between 0.51 and 1.39, p < 0.0001, 2 studies,
- final height (cm): WMD = 5.50, 95% CI between 2.73 and 8.28, p < 0.0001, 2 studies.

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\(^3\) WMD : weighted mean difference.
- change of height SDS: WMD = 0.53, 95% CI between 0.30 and 0.75, p < 0.0001, 2 studies, and
- change of growth rate SDS: WMD = 0.93, 95% CI between 0.50 and 1.37, p < 0.0001, 2 studies.

Observational studies
In the studies in the Turner syndrome cohort identified by HAS, it is observed that growth hormone treatment increases the adult height reached by the girls by 6 or 7 cm compared with the projected adult height. According to these studies, they should reach a height of about 150 cm (varies according to country). However, this increase in height varies between 3 and 17 cm, depending on the cohort. Nevertheless, even though girls who are treated become taller than untreated girls, their height remains lower than normal (< -2 SDS). Even though the results of these studies do not prove the efficacy of growth hormone in respect of adult height, they are nevertheless compatible with the increase in adult height observed in the meta-analysis.

6.1.2. Chronic renal disease
Meta-analysis of clinical studies
In renal disease, the meta-analysis commissioned by HAS identified 13 randomised studies, with 16 comparisons and a total of 665 patients. The comparisons carried out were:
- growth hormone (GH) versus placebo,
- GH versus untreated,
- high dose (56 IU/m²/week) versus low dose (28 IU/m²/week),
- high dose (28 IU/m²/week) versus low dose (14 IU/m²/week).

In addition to the studies included, five clinical studies that gave rise to six publications were excluded for the following reasons: study not randomised, analysis together with unusable data and subgroup of another study. No studies that were in progress at the time were identified by checking the registers and other sources.

The mean population was 41 patients per group (between 3 and 82 per group). The first study was published in 1991, the last in 2002. Five studies were double blind and 10 were open. All the studies included were reported in English, except one which is in Japanese. No unpublished studies were identified.

The data related to the following criteria:
- growth rate (1 year) (11 studies),
- change of height SDS (9 studies),
- change of growth rate SDS (7 studies),
- change of growth rate (cm/year) (4 studies),
- height at the end of the study SDS (4 studies),
- growth rate SDS (3 studies),
- change of height (cm) (1 study).

In the GH versus placebo comparison, GH was better than placebo in terms of:
- height at end of study SDS: WMD = 1.36, 95% CI between 0.86 and 1.86, p < 0.0001, 1 study,
- change of height SDS: WMD = 1.18, 95% CI between 0.74 and 1.62, p < 0.0001, 1 study,
- growth rate (1 year): WMD = 4.20, 95% CI between 2.92 and 5.48, p < 0.0001, 1 study,
- change of growth rate SDS: WMD = 7.80, 95% CI between 6.09 and 9.51, p < 0.0001, 2 studies.

In the GH versus untreated comparison, GH was better than untreated in respect of:
- height at end of study SDS: WMD = 0.73, 95% CI between 0.33 and 1.12, p < 0.0001, 3 studies,
- change of height (cm): WMD = 3.80, 95% CI between 2.51 and 5.09, p < 0.0001, 1 study,
- change of height SDS: WMD = 0.72, 95% CI between 0.51 and 0.93, p < 0.0001, 4 studies.

4: WMD: weighted mean difference.
- growth rate (1 year): WMD = 3.76, 95% CI between 3.12 and 4.39, p < 0.0001, 6 studies,
- change of growth rate SDS: WMD = 6.14, 95% CI between 3.42 and 8.86, p < 0.0001, 2 studies.

In the high dose (56 IU/m²/week) versus low dose (28 IU/m²/week) comparison, no statistically significant difference was observed in terms of:
- change of height SDS: WMD = 0.30, 95% CI between -1.00 and 1.60, p = 0.6522, 1 study,
- growth rate (1 year): WMD = 1.10, 95% CI between -1.23 and 3.43, p = 0.3543, 1 study,
- change of growth rate (cm/year): WMD = 1.10, 95% CI between -1.23 and 3.43, p = 0.3543, 1 study.

In the high dose (28 IU/m²/week) versus low dose (14 IU/m²/week) comparison, no statistically significant difference was observed for change of height SDS (WMD = 0.17, 95% CI between -0.14 and 0.49, p = 0.2784, 3 studies). Nevertheless, the high dose (28 IU/m²/week) is better than the low dose (14 IU/m²/week) in terms of:
- growth rate (1 year): WMD = 1.34, 95% CI between 0.55 and 2.13, p < 0.0001, 3 studies,
- growth rate SDS: WMD = 1.30, 95% CI between 0.30 and 2.30, p = 0.0108, 3 studies,
- change of growth rate (cm/year): WMD = 1.34, 95% CI between 0.55 and 2.13, p < 0.0001, 3 studies,
- change of growth rate SDS: WMD = 1.30, 95% CI between 0.30 and 2.30, p = 0.0108, 3 studies.

According to data from North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2006 (Appendix 8), growth hormone is used in less than 6.5% of patients with chronic renal disease at the time of inclusion in the register. After monitoring for 24 months, the figure is 15.9%.

Observational studies
In the observational studies analysed, an increase in adult height of more than 2 SD was observed in 40 to 50% of cases. Even though the results of these studies do not prove the efficacy of growth hormone in respect of adult height, they are nevertheless compatible with the increase in adult height observed in the meta-analysis. In these studies, the increase in height depends on the age at the start of treatment or its duration, in particular with respect to the onset of puberty, the residual renal function and the initial growth failure.

6.2. Clinical relevance of the observed effect level in the studies
In adults, one standard deviation (SD) in height represents 5.6 cm (women) or 6 cm (men).

The effect of growth hormone on final height has been evaluated as +1.15 SD in Turner syndrome, which is about 6.5 cm and as +0.6 SDS, or about 3.4 to 3.5 cm, in SGA.

In these two indications, Turner syndrome and SGA, the final heights of the patients remain within the lower limits of the normal range.

The effect of growth hormone on final height in Prader-Willi syndrome or in chronic renal disease is not known.

In the absence of treatment, the epidemiological data indicate that the mean adult height for the various indications concerned is 1 m 43 (Turner syndrome), 1 m 65 for men and 1 m 54 for women (children born small for gestational age who failed to show catch-up growth by the age of 4 years), 1 m 54 for men and 1 m 45 – 1 m 49 for women (Prader-Willi syndrome), 1 m 56 for men and 1 m 52 for women (chronic renal disease).

Moreover, the appreciated benefits of treatment are evaluated with regard to additional adult height and height attained in cm. However, it seems reasonable to ask whether the appreciated benefit differs as a function of adult height: the value of an increase of 1 cm could be greater in individuals of small height than in those who reach normal weight or who are tall. Failure to take into account the relative value of the increase in adult height is equivalent to underestimation of the benefit of the treatment to the patients.

Equally, it could be thought that an increase in adult height acquired during childhood would continue to be of benefit to the patient throughout his or her life and not simply at the time he or she reaches adult height. Failure to take into account the long-term benefit could be
equivalent to underestimation of the benefit of treatment as experienced by the patient throughout his or her life.

6.3. **Long-term tolerance**

**Epiphysiolysis**

During the course of treatment, growth hormone may involve rare but serious risks. Epiphysiolysis of the femoral head has been described in all indications, but especially in growth hormone deficiency. This may be responsible for prolonger immobilisation and its sequellae.

**Risk of diabetes**

It is suspected that there a risk of the development of long-term diabetes some time after the discontinuation of treatment because of metabolic disorders (frequent hyperinsulinaemia, occasional hyperglycaemia) that develop under treatment and which are reversible after the discontinuation of treatment. However, no studies disprove or confirm an effect of growth hormone.

**Risk of cancer**

In respect of the risk of cancer, even though the publically available data do not permit formal confirmation of an increased risk of death from and/or the occurrence of cancer due to growth hormone in non-deficient children compared with the general population, they do not disprove it either.

**Risk of mortality**

In November 2010, the results of the French SAGHE study to evaluate mortality and long-term morbidity in children exposed to growth hormone were presented. These are unpublished data made public by Afssaps in December 2010. The presentation of this study led to the reassessment of the benefit-risk ratio of growth hormone by the EMA in May 2011 and by the FDA in April 2011, which was confirmed as favourable.

This is an unpublished observational study, carried out on the basis of the French pituitary registry, which contains data on more than 10000 young adults who received treatment with recombinant growth hormone during childhood between 1985 and 1996.

The analysis, which was carried out in patients with growth failure due to an isolated growth hormone deficiency (about 75% of the patients) or of short stature of unexplained origin (with or without prenatal growth restriction) relates to almost 7000 patients in the registry, showed an excess risk of mortality of all causes together of 93 deaths versus 70 expected in a reference population in France.

This risk is particularly high in patients who received high doses, above those recommended in the current Marketing Authorisation. The data do not show any increase in global mortality due to cancer (all cancers together). They do, however, suggest increased mortality due to the occurrence of cerebrovascular complications (such as intracerebral haemorrhages) and bone cancers.

The observational nature of these results does not permit the establishment with certainty of a causal relationship with the treatment with growth hormone.

Mortality in the group of patients with renal disease, Turner syndrome, Prader-Willi syndrome or GH deficiency secondary to a tumour was not the subject of this analysis.

Even though these results constitute a signal, the design and nature of the study means that they do not establish a causal relationship between mortality and the GH treatment. Other factors may be associated with the increased mortality observed in the population studied.

Taking into consideration the French SAGHE study, the EMA and the FDA concluded that the benefit-risk relationship is still favourable, that strict observation of the indications is necessary, that the doses in the Marketing authorisation must not be exceeded, and that it is

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5 One study carried out in patients, most of whom were deficient, treated which growth hormone obtained by extraction, concluded that there was the risk of colorectal cancer and Hodgkin’s lymphoma is 15 times higher in patients with no history of cancer or identified cancer risk factors compared with the general population of the same age.
necessary to wait, before reaching a definitive conclusion, for the results of the European SAGHE study.

Specific risks in each of the indications in non-deficient children

Turner syndrome

An increase in the frequency of otitis under treatment with GH was noted in two of the three clinical studies. The other events observed (scoliosis, dysthyroidism, glucose intolerance, aortic dissection, pericarditis, cardiac insufficiency, arterial hypertension, lymphoedema, thyroid abnormality etc.) are those of the natural development of the illness, and no effect of GH was specifically isolated. However, it was not possible to exclude an increase in these events due to GH.

Chronic renal disease

In one study in children with CRD, on dialysis or after transplantation, the use of GH was associated with an increased risk of lymphoproliferative syndromes.

6.4. Is small stature a pathological condition?

Whether small stature is a pathological condition depends on the theoretical framework within which it is placed.

According to the first definition, a pathological condition is conceived as a state in which organic or mental functioning is disturbed. Short stature (in the absence of growth hormone deficiency) would thus not constitute a pathological condition to the extent that no dysfunction has been identified. Nevertheless, it should be noted that there is an association between height and a substantial number of medical conditions, but that the nature of these associations and the underlying mechanisms are poorly understood.

According to the second definition, a pathological condition is defined as a physical or mental process that tends to affect the wellbeing of the individual such as his or her ability to act and achieve his or her objectives within his or her environment. From this point of view, short stature could be considered a pathological condition if it affects an individual to the point of disturbing his or her global development in a physical, psychological and social sense.

No data have been identified in the literature that demonstrate a difference at a psychological level in social adjustment between children of short stature and children of normal stature of the same age in the general population even though children of small stature referred for specialist consultations (and treated if appropriate) for that reason may have been affected in a pronounced way at a psychological and social level by their short stature (compared with children of short stature who have not been referred and/or are not treated). However, the quality of life of children of short stature remains better that of children suffering from other conditions (chronic illnesses, for example) and, even if the self-esteem is the area of the quality of life most affected (in particular during adolescence), it is difficult to deduce the magnitude of the impact of short stature on the quality of life of young children. Thus, in the second definition, it appears that short stature does not necessarily assume a pathological nature for all children, but it may do so at an individual level when the effect is pronounced.

There is also a need to consider the whether, and to what extent, the pathological character of short stature varies as a function of the individual characteristics of the patient. Short stature could be considered pathological on the grounds that the patient is also suffering from a well-identified illness of known aetiology (Turner syndrome, Prader-Willi syndrome, chronic renal disease), has a genetic abnormality that may be associated with short stature, but which is of poorly understood clinical significance (SHOX deficiency), or, finally, if it corresponds to a descriptive definition (small for gestational age)? If appropriate, short stature could be considered pathological in certain patients and as non-pathological in others who do not present the same individual characteristics, irrespective of their height and its impact on the quality of life and wellbeing.

6.5. Conclusion

The results of the meta-analysis of final height show:

in Turner syndrome, an increase in height versus untreated of +1.15 SDS [0.73; 1.57], or of the order of +6.5 cm.

in chronic renal disease, the final height is not available; instead, the target variable is the increase in height under GH before transplantation. The increase in height under GH versus untreated at the end of the study is +0.73 [0.33;1.12].
The results of the available observational studies are similar.

In terms of tolerance, there is a signal relating to increased mortality due to growth hormone, a suspected dose-related effect, but supplementary studies are still required to reach a formal conclusion.

The Committee wants the use of growth hormones to follow good practice, that is to say:
- limitation of prescriptions to the strict indications of the Marketing Authorisation,
- compliance with the dosages,
- discontinuation after one year of treatment in no responders (growth rate < 1 SD or < 2 cm/year). Growth hormone treatment should always be re-evaluated after one to two years of treatment, when there is sufficient information to review the course of growth.
- the greatest caution still needs to be taken when deciding to commence and when monitoring GH treatment.
7.1. Reassessment of actual benefit

**Growth failure due to Turner syndrome:**

Turner syndrome of genetic origin is a rare illness associated with short stature, dysmorphic features, problems with pubertal development and fertility, malformation of certain organs (heart, vessels, kidneys in particular) and an increase in cardiovascular mortality.

This proprietary medicinal product falls within the framework of a curative treatment of short stature, integrated in global treatment of the illness.

The efficacy of growth hormone on adult height in Turner syndrome has been demonstrated in one study and confirmed in other studies with different height parameters. The increase in height is modest. Observational studies confirm the efficacy that was observed in the clinical studies.

There is a tolerance signal suggesting increased mortality in adults who have used growth hormone during childhood. Supplementary studies are required to reach a conclusion.

The efficacy/adverse effects ratio of this propriety medicinal product is modest in this indication.

There are no alternative medicinal treatments to somatropin that have an effect on height.

**Public health benefit:**

Growth failure in children due to Turner syndrome is a minor burden in terms of public health in view of the limited number of patients involved.

This illness falls within the category of rare illnesses, its treatment is a public health need (Second National Rare Diseases Plan, 2010-2014).

This illness requires global, multidisciplinary treatment, and treatment with growth hormone is just one of these aspects.

According to the available data, the effect of growth hormone treatment on the final height of the children is at most moderate. The impact at the psychological, social and quality of life level has not been established.

Moreover, a negative effect cannot be ruled out, particularly because searches indicate the long-term risk of the occurrence of cancer, diabetes and cardiovascular diseases.

In addition, there is no guarantee that the data from clinical studies can be transposed to clinical practice, particularly in view of the observance problems linked to the long-term need for daily injections.

As a result, growth hormone treatment will not provide any public health benefit in the treatment of growth failure in girls with Turner syndrome confirmed by chromosome analysis.

Taking into account all the data studied, the actual benefit of NUTROPINAX in Turner syndrome is **substantial.**
**Growth failure due to chronic renal disease:**
Chronic renal disease in children is a rare but serious illness with a variable course, depending on the aetiology, and can sometimes lead to the death of the child. Short stature is just one feature of this illness, and may contribute to a marked deterioration of the quality of life.

This proprietary medicinal product falls within the framework of a curative treatment of short stature, integrated in global treatment of the illness.

The efficacy of growth hormone on height at the end of the study in chronic renal disease has been demonstrated, and confirmed in other studies with different height parameters. Observational studies confirm the efficacy that was observed in the clinical studies. During the short period of the study before the transplant, the increase in height is small, but forms part of the necessary global treatment.

There is a tolerance signal suggesting increased mortality in adults who have used growth hormone during childhood. Supplementary studies are required to reach a conclusion.

The efficacy/adverse effects ratio of this propriety medicinal product is modest in this indication.

There are no alternative medicinal treatments to somatropin that have an effect on height.

**Public health benefit:**
Growth failure in children due to chronic renal failure is a minor burden in terms of public health in view of the limited number of patients involved.
This illness falls within the category of rare illnesses, its treatment is a public health need (Second National Rare Diseases Plan, 2010-2014).
This illness requires global, multidisciplinary treatment, and treatment with growth hormone is just one of these aspects.
According to the available data, the effect of growth hormone treatment on the height of the children is at most moderate. The effect of the treatment on adult height has not been established. The impact at the psychological, social and quality of life level has not been established.
Moreover, a negative effect cannot be ruled out, particularly because searches indicate the long-term risk of cancer, diabetes and cardiovascular diseases.
In addition, there is no guarantee that the data from clinical studies can be transposed to clinical practice, particularly in view of the observance problems linked to the fairly long-term need for daily injections.
As a result, growth hormone treatment will not provide any public health benefit in the treatment of growth failure due to chronic renal disease.

Taking into account all the data studied, the actual benefit of NUTROPINAQ in chronic renal disease is **substantial**.

**7.2. Improvement in actual benefit (IAB)**
NUTROPINAQ provides about a minor improvement in actual benefit (IAB IV) in the treatment of Turner syndrome and chronic renal disease.
7.3. Target population

Estimates of the size of maximum theoretical prevalent target populations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimate</th>
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<tbody>
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<td>Turner syndrome</td>
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</tr>
<tr>
<td>Chronic renal insufficiency</td>
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</table>

7.4. Transparency Committee recommendations

The transparency Committee recommends continued inclusion of NUTROPINAQ on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in children with Turner syndrome or chronic renal insufficiency.

7.4.1. Packaging: Appropriate for the prescription conditions in the Marketing Authorisation

7.4.2. Reimbursement rate: 65 %