Review of the dossier for proprietary medicinal products included for a 5-year period starting on 07.08.2007 (Official Gazette of 05.05.2009)

**SAIZEN 1.33 mg/ml, powder and solvent for solution for injection**  
B/1 vial of 1 ml (CIP: 341 930-8)

**SAIZEN CLICKEASY 8 mg/1.37 ml, multiple dose powder and solvent for solution for injection**  
B/1 cartridge of 1.37 ml (CIP: 356 761-2)

**SAIZEN 5.83 mg/ml, solution for injection**  
B/1 cartridge of 1.03 ml (CIP: 415 574-5)

**SAIZEN 8 mg/ml, solution for injection**  
B/1 cartridge of 1.50 ml (CIP: 415 576-8)

**SAIZEN 8 mg/ml, solution for injection**  
B/1 cartridge of 2.50 ml (CIP: 415 577-4)

**Applicant: MERCK SERONO**

somatropin

ATC code: H01AC01 (ANTERIOR PITUITARY LOBE HORMONES AND ANALOGUES)

**List I**  
Initial annual hospital prescription restricted to specialists in paediatrics and/or endocrinology and metabolic diseases practising in specialized paediatric and/or endocrinology and metabolic diseases departments.

Date of Marketing Authorisation (mutual recognition procedure, rapporteur country Italy)  
SAIZEN 1.33 mg/ml: 3 April 1989  
SAIZEN CLICKEASY: 17 December 1998

**Reason for request:** Renewal of inclusion on the list of proprietary medicinal products reimbursed by National Health Insurance.

Medical, Economic and Public Health Assessment Division
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Somatropin

1.2. Indications

Children

- Treatment of growth failure in children caused by decreased or absent secretion of endogenous growth hormone
- Treatment of growth failure in girls with gonadal dysgenesis (Turner Syndrome), confirmed by chromosomal analysis.
- Treatment of growth failure in prepubertal children due to chronic renal failure (CRF).
- Treatment of growth failure (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS <0 during the last year) by 4 years of age or later.

In adults

- Replacement therapy in adults with pronounced growth hormone deficiency as diagnosed by a single dynamic test for growth hormone deficiency. Patients must also fulfil the following criteria:
  - Childhood Onset: Patients who were diagnosed as growth hormone deficient during childhood, must be retested and their growth hormone deficiency confirmed before replacement therapy with SAIZEN is started.
  - Adult Onset: Patients must have growth hormone deficiency as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) and adequate replacement therapy instituted, before replacement therapy using growth hormone may begin.

1.3. Dosage

- Growth hormone deficiency in children: 0.025 – 0.035 mg/kg/day (i.e. 0.7 to 1.0 mg/m²/day)
- Turner syndrome: 0.045 – 0.050 mg/kg/day (i.e. 1.4 mg/m²/day)
- Chronic renal impairment: 0.045 – 0.050 mg/kg/day (i.e. 1.4 mg/m²/day)
- Children born small for gestational age: 0.035 mg/kg/day (i.e. 1.0 mg/m²/day)

- Growth hormone deficiency in adults: 0.15 – 0.30 mg/day (i.e. 1.0 mg/m²/day). The dose should then be gradually adjusted and monitored by means of serum levels of growth factor (IGF-1).
### 2 SUMMARY OF THE TRANSPARENCY COMMITTEE’S PREVIOUS OPINIONS

#### Table 1: AB of growth hormone proprietary medicinal products in the indications of UMATROPE

<table>
<thead>
<tr>
<th></th>
<th>GH deficiency in children</th>
<th>GH deficiency in adults</th>
<th>Turner syndrome</th>
<th>Chronic renal insufficiency in prepubertal children</th>
<th>SHOX gene deficit</th>
<th>Children born small for gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTONORM</td>
<td>substantial</td>
<td>moderate</td>
<td>substantial</td>
<td>substantial</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>NORDITROPIN</td>
<td>substantial</td>
<td>moderate</td>
<td>substantial</td>
<td>substantial</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>NUTROPIAQAQ</td>
<td>substantial</td>
<td>moderate</td>
<td>substantial</td>
<td>substantial</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SAIZEN</td>
<td>substantial</td>
<td>moderate</td>
<td>substantial</td>
<td>substantial</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>UMATROPE</td>
<td>substantial</td>
<td>moderate</td>
<td>substantial</td>
<td>substantial</td>
<td>moderate</td>
<td>low</td>
</tr>
<tr>
<td>ZOMACTON</td>
<td>substantial</td>
<td>-</td>
<td>substantial</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>substantial</td>
<td>moderate</td>
<td>substantial</td>
<td>substantial</td>
<td>low</td>
<td></td>
</tr>
</tbody>
</table>

*The Transparency Committee has restricted the scope of the AB when height is < -3 SD while the marketing authorisation concerns heights <-2.5 SD.*

#### Table 2: IAB of growth hormone preparations in the indications of UMATROPE

<table>
<thead>
<tr>
<th></th>
<th>GH deficiency in children</th>
<th>GH deficiency in adults</th>
<th>Turner syndrome</th>
<th>Chronic renal insufficiency in prepubertal children</th>
<th>SHOX gene deficit</th>
<th>Children born small for gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUTROPIAQAQ</td>
<td>V (Sept 2004)</td>
<td>V (Sept 2004)</td>
<td>IV (Dec 2011)</td>
<td>IV (Dec 2011)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ZOMACTON</td>
<td>II (Oct 1996)</td>
<td>-</td>
<td>IV (Dec 2011)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>V (Jan 2007)</td>
<td>V (Jan 2007)</td>
<td>IV (Dec 2011)</td>
<td>IV (Dec 2011)</td>
<td>-</td>
<td>V (Dec 2011)</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: Anterior pituitary lobe hormones and analogues
H01AC: Somatropin and analogues
H01AC01: Somatropin

3.2. Medicines in the same therapeutic category
These are proprietary medicinal products of human recombinant growth hormone or somatropin (rh-GH).

Table 4: Indications for proprietary medicinal products containing growth hormone

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTONORM</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>no</td>
<td>+</td>
</tr>
<tr>
<td>NORDITROPIN</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>+</td>
</tr>
<tr>
<td>NUTROPINAQ</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>SAIZEN</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>ZOMACTON</td>
<td>+</td>
<td>no</td>
<td>+</td>
<td>no</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>+</td>
<td>+</td>
<td>no</td>
<td>+</td>
</tr>
</tbody>
</table>

3.3. Medicines with a similar therapeutic aim
none.
According to EGB data extrapolated to the French population, the number of patients who received at least one dispensed prescription for growth hormone in 2011 is estimated to be 17,607 (95% CI [14,888; 20,327]). The distribution per proprietary medicinal product is presented in Table 1.

Table 1: Number of patients with at least one dispensed prescription for growth hormone in 2011 according to EGB data extrapolated to the French population

<table>
<thead>
<tr>
<th>Proprietary medicinal product</th>
<th>Number (%</th>
<th>Number extrapolated to the French population</th>
<th>95% CI Lower limit</th>
<th>95% CI Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTONORM</td>
<td>44 (27)</td>
<td>4812</td>
<td>3390</td>
<td>6234</td>
</tr>
<tr>
<td>NORDITROPIN SIMPLEXX</td>
<td>41 (25)</td>
<td>4484</td>
<td>3111</td>
<td>5856</td>
</tr>
<tr>
<td>NUTROPINAQ</td>
<td>22 (14)</td>
<td>2406</td>
<td>1401</td>
<td>3411</td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>13 (8)</td>
<td>1422</td>
<td>649</td>
<td>2195</td>
</tr>
<tr>
<td>SAIZEN</td>
<td>19 (12)</td>
<td>2078</td>
<td>1144</td>
<td>3012</td>
</tr>
<tr>
<td>UMATROPE</td>
<td>20 (12)</td>
<td>2187</td>
<td>1229</td>
<td>3146</td>
</tr>
<tr>
<td>ZOMACTON</td>
<td>3 (2)</td>
<td>328</td>
<td>-43</td>
<td>699</td>
</tr>
<tr>
<td>Total</td>
<td>161</td>
<td>17,607</td>
<td>14,888</td>
<td>20,327</td>
</tr>
</tbody>
</table>

The median age of the patients was 14 years (minimum: < 1 year; maximum: 68 years). The distribution of patients by age and gender is presented in Table 2.

Table 2: Distribution of patients by age and gender

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>21 (54)</td>
<td>18 (46)</td>
<td>39 (24)</td>
</tr>
<tr>
<td>[10-14]</td>
<td>22 (58)</td>
<td>16 (42)</td>
<td>38 (24)</td>
</tr>
<tr>
<td>[14-17]</td>
<td>23 (68)</td>
<td>11 (32)</td>
<td>34 (21)</td>
</tr>
<tr>
<td>[17-25]</td>
<td>4 (57)</td>
<td>3 (43)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>&gt;=25</td>
<td>18 (42)</td>
<td>25 (58)</td>
<td>43 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>88 (55)</td>
<td>73 (45)</td>
<td>161 (100)</td>
</tr>
</tbody>
</table>

4 values missing; * % in rows; † % in columns

The EGB is a representative sample (1/97) from all health insurance beneficiaries. It contains anonymous information about the demographic characteristics of those persons, the benefits paid and chronic (long-term) conditions since 2003. The extrapolation of EGB data to the French population was done by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries in the EGB on 01.01.2011 (n = 594,370) in relation to the French population on 01.01.2011 (n = 65,001,181). The extrapolation coefficient obtained is 1/109.36.
5 CONTEXT OF THE EVALUATION

Presented below are New data for somatropin-based recombinant human growth hormone (rh-GH) proprietary medicinal products indicated in children and adults with GH deficiency, obtained since the previous re-listing of an rh-GH proprietary medicinal product by the Transparency Committee in 2007 and the re-evaluation in non-deficient children since the opinion of December 7, 2011.

6 RE-EVALUATION OF rh-GH IN NON-DEFICIENT CHILDREN

In December 2011, the Committee re-evaluated the AB and IAB of all rh-GH proprietary medicinal products indicated in non-GH-deficient children (short stature associated with Turner syndrome, chronic renal impairment, Prader Willi syndrome, SHOX gene deficiency or in children born small for gestational age), on the basis of the HAS report “Growth hormone in non-deficient children” (available at http://www.has-sante.fr). The new data obtained since the opinion of December 7, 2011 do not change the Committee’s previous conclusions.

7 RE-EVALUATION OF rh-GH IN DEFICIENT CHILDREN

7.1. GH deficiency in children

Half of all cases of growth hormone deficiency in children are of unknown origin. Other cases may be secondary to an organic disease, such as tumour of the brain, or of the hypothalamic-pituitary, to a cranio-spinal or whole body irradiation or may be congenital in origin. The GH deficiency may occur on its own or be associated with other pituitary deficiencies.

For rh-GH to be prescribed, the diagnosis of growth hormone deficiency must be confirmed by means of two separate stimulation tests performed on different days, of which at least one must be a joint test (e.g. insulin/arginine).

7.2. Reminder of initial efficacy results

In 1996, reimbursement of rh-GH was permitted for the first time for deficiency in children. Data available at the time showed an increase in height at the end of trial of the order of +1 to +2 SDS over a maximum trial duration of 3 years.

7.3. New data

New data for GH deficiency in children supplied by the pharmaceutical companies are presented company by company in Appendix 1.
Of these, the following relate to adult height or to treatment of prolonged duration:

- long-term follow-up data in the form of follow-up of the cohort of all treated patients.
  - the KIGS cohort\(^2\) (see Appendix 1) of patients treated with GENOTONORM. In this cohort, the increase in height from the start to the end of treatment was +1.5 to +2.5 SDS according to the aetiology of the GH deficit, except in the case of malignant tumours, where the height remained stable at -0.1 SDS.
  - the GENESIS cohort (see Appendix 1) of patients treated with UMATROPE. These are observational data from monitoring during the course of treatment, which were collected by LILLY. In this cohort, the gain in height from the start to the end of treatment was + 1.44 ± 1.18 SDS for patients treated until adulthood (1439/9697 of the cohort) (unpublished data).

These data demonstrate the limits of an observational, non-comparative cohort, with many members lost to follow-up, particularly with follow-up being stopped on discontinuation of treatment. They do however enable the gain in height at adulthood to be confirmed, even though the size of this gain is overestimated, because it was measured solely for those children who had been treated the longest.

- cohort studies on small groups also analysed adult height:
  - extracts from the France Hypophyse register\(^3\) for 44 patients treated for a period of more than 14 years with rh-GH until attaining adult height. At a mean age of 22 years, the mean height was -0.3 SDS ± 1.3 with the expected height being -0.4 SDS ± 0.8).
  - Non-comparative retrospective study by Rachmiel\(^4\) who analysed the adult heights of 96 children treated with rh-GH. The results showed that 84% of children reached a normal adult height, which was greater than -2 SDS (-1.04 ± 1.00 SDS), with a gain in height of +1.8 ± 1.2 SDS.

- A 7-year open-label clinical trial of OMNITROPE versus GENOTONORM\(^5\) in childhood deficiency did not show any difference in height between the groups. The gain in height after 7 years of treatment was of the order of +2 SDS.

- In addition, other clinical trials and cohort follow-ups of shorter duration were supplied. Of these, two trials complete the data on height:
  - The clinical trial conducted by Salerno\(^6\) compared, in an open-label design, biological cardiovascular risk factors between a treated group and an untreated group and showed an improvement in the lipid profile in treated patients (total cholesterol 3.5 mmol/l ± 0.1 in the treated group vs. 4.2 mmol/l ± 0.1 in the untreated group, p < 0.0001).
  - The study by Coelho\(^7\) showed that increasing dosage during puberty had no significant effect on the final height of patients with a GH deficiency.

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\(^1\) Growth Hormone Therapy in Pediatrics – 20 years of KIGS. Michael B Ranke, David A Price, Edward O Reiter. 2007, chap 3, 10, 11 and 17


7.4. Clinical Practice Guidelines

No recent guideline has been published in France concerning the treatment of children with growth hormone deficiency.

In the United Kingdom, rh-GH was re-evaluated by NICE in 2010\(^8\) with respect to children with growth hormone deficiency. In terms of efficacy, the gain in final height is estimated in this report to be between 8 and 11 cm in children with growth hormone deficiency.

7.5. Tolerance

A risk of cancer associated with the use of rh-GH was suspected due to the mechanism of action of IGF-1, the principal growth hormone mediator, which stimulates the cell growth and proliferation and inhibits apoptosis (programmed cell death).

Since the clinical trials, pharmacovigilance data and first epidemiological studies did not enable the reality of this risk to be determined, two new epidemiological studies were conducted at the French and European levels and published in 2012. These studies primarily concern subjects with a deficiency.

7.5.1. Santé Adulète GH Enfant (SAGhE)\(^9\) French study

This is an observational study published in January 2012, which is based on the France-Hypophyse register established by the Agence nationale de sécurité des médicaments (ANSM, National Agency for the Safety of Pharmaceuticals and Health Products) in partnership with the Directorate-General for Health (DGS) and the National Cancer Institute (INCa), the objective of which was to obtain data on long-term risk in young adults, who had received biosynthetic growth hormone in childhood.

The analysis was conducted on 6928 patients aged over 18 years, who had been treated as children with growth hormone in the period 1985-1996. The patients included were those with an isolated idiopathic deficiency (n = 5162), a neurosecretory dysfunction (n = 534) and also those with idiopathic short stature (n = 871) and children born small for gestational age (n = 335).

The results showed an excess risk of all-cause mortality with 93 deaths occurring versus the 70 deaths expected in a reference population of normal height in France. This corresponds to a standardized mortality ratio (SdMR) = 1.33 (95% CI: [1.08 – 1.64]). In a multivariate analysis adjusted for height, the use of doses greater than 50 µg/kg/day was associated with an increased mortality (SdMR = 2.94 95% CI: [1.22 – 7.07]). There was no increase in deaths from cancer of all types. However, mortality due to bone cancer was increased (SdMR = 5.00 95% CI: [1.01 – 14.63]) as well as mortality due to vascular system disease (SdMR = 3.07 95% CI: [1.40-5.83]) especially due to meningeal or intracerebral haemorrhage (SdMR = 6.66 95% CI: [1.79 – 17.05]). In these latter two cases, numbers were very low (three deaths due to bone cancer and four due to cerebrovascular causes).

7.5.2. Preliminary results of the European SAGhe study

The SAGhe study was subsequently extended to several European countries:\(^10\) Belgium, The Netherlands and Sweden. The study was conducted in the same way as the French SAGhE

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\(^8\) TA188 Human growth hormone (somatropin) for the treatment of growth failure in children: guidance - 22 July 2010 - guidance.nice.org.uk


study, being based on registers of children treated with rh-GH in each of the countries studied. The causes of death were collected from available sources in a different way in each country.

The analysis was conducted on 2543 adults aged over 18 years, who had been treated as children with growth hormone in the period 1985-1997. They were patients with an isolated deficiency, idiopathic short stature or infants born small for gestational age.

The results showed that of the 21 deaths that were identified, 12 were due to accidents, 4 were suicides and 1 patient died of lung disease with multiple organ failure. No cancer was identified.

7.5.3. Other safety data

According to the SPC, the following adverse effects occur over the medium term in children with or without an underlying deficiency disease:

- **Headaches (rare) and benign intracranial hypertension (rare), generally at start of treatment, disappearing gradually on discontinuation of treatment.**
- **Fluid retention (uncommon): may result in peripheral oedema, stiffness, arthralgia, myalgia, paraesthesia. These effects are generally transitory and dose-dependent.**
- **Epiphysiolysis of the femoral head (epiphysiolysis capitis femoris) or necrosis of the femoral head (rare). This occurs more frequently at the start of treatment and in patients with a deficiency.**
- **Occurrence of anti-somatotropin antibody (uncommon). No clinical changes have been associated with the presence of these antibodies.**
- **Insulin resistance can lead to hyperinsulinaemia and, in rare cases, to hyperglycaemia and diabetes.**

The periodic safety update reports supplied by the companies identified two new unexpected adverse effects which could be attributed to the treatment:

- Errors in dosage due to confusion between the presentation of NORDIPEN and NORDITROPIN Simplexx. The SPC was not amended.
- “an increased risk of a second neoplasm (malignant or benign) was reported in patients treated with somatotropin who had survived cancer in childhood. Intracranial tumours, in particular, were the most common of these second neoplasms.” This warning was added in section 4.4 of the SPC for UMATROPE in June 2011. It should be noted that the same statement exists for NUTROPINAQ.

The results of follow-up studies submitted by the companies did not reveal any new pharmacovigilance problems.

7.6. Conclusion for data on children deficient in GH

The studies supplied by the companies confirmed the initial results with respect to efficacy on the height of children with growth hormone deficiency.

The new adverse effects in the PSUR and follow-up studies (errors in dosage and increased risk of second neoplasm) do not change the safety profile of rh-GH.

In a French epidemiological study (SAGHÉ), an increased mortality (SdMR = 1.33) was observed in adults who had been treated with rh-GH during childhood. Most of these patients had GH

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11 PSUR GENOTONORM 11 August 2004 to 31 March 2008
PSUR SAIZEN: 8 March 2011 to 7 March 2012
PSUR OMNITROPE: 28 March 2011 to 29 February 2012
PSUR NORDITROPIN: 1 April 2010 to 31 March 2012
PSUR NUTROPINAQ: 16 February 2009 to 15 February 2012
PSUR ZOMACTON: 1 April 2008 to 31 March 2009 and April 2009 to 1 November 2009
PSUR umatrope: 9 April 2010 to 31 March 2011
deficiency. This finding was not confirmed in the preliminary results from the European SAGhE study. Additional results are awaited.

In summary, these data do not change the evaluation of actual benefit provided by rh-GH in GH deficiency in children compared to that in the previous opinion issued by the Transparency Committee on 16 November 2005.

8 RE-EVALUATION OF rh-GH IN DEFICIENT ADULTS

8.1. GH deficiency in adults

GH deficiency in adults may be associated either with a deficiency in childhood, which has become prolonged into adulthood, or, more often, with an deficiency acquired after adolescence, which is either idiopathic or secondary to a tumour of the pituitary (adenoma is the most common cause) or of the region surrounding the pituitary or, more rarely, secondary to severe cranial trauma. GH deficiency is often associated with other hormonal deficiencies.

Clinically, adults with GH deficiency present metabolic and lipid abnormalities, altered body composition (increased body fat and decreased lean mass), decreased bone density and decreased muscle strength. They also show psychosocial disorders, associated particularly with mental and physical asthenia.

The objective of growth hormone therapy is to influence the quality of life, body composition, lipid factors and cardiovascular risk.

According to the international guidelines published in 2007, GH deficiency is defined biochemically. However, a deficiency should not be investigated outside of an indicative clinical context.

A single stimulation test indicating a deficiency is sufficient to establish the diagnosis. Patients with three deficiencies or more in pituitary hormones and a decreased level of IGF1 have a 97% risk of GH deficiency and no stimulation test is required to confirm the diagnosis.

8.2. Reminder of initial results for growth hormone efficacy

In 1996, in the course of the first request for listing of GENOTONORM and NORDITROPIN in the indication of adult deficiency, the randomised, double-blind, placebo-controlled studies were of a maximum 12 months in duration. They had been complemented by open-label studies in adult patients with deficiencies of various aetiologies (deficiencies since childhood or acquired in adulthood) and substituted for other pituitary disorders if necessary.

The conclusions were that treatment with rh-GH:
- tends to normalise the muscle mass/fat mass distribution
- has a significant positive effect in increasing bone mineral density without demonstrated efficacy in preventing the occurrence of fractures,
- significantly improves the quality of life according to criteria based on perceived general condition and well being.

The Committee did not recommend listing in this indication in adults.

In 1997, the firm presented the existing data in the context of the severity of problems of morbidity and morbidity/mortality in individuals with pituitary insufficiency. The Committee requested new efficacy and safety data and suggested a meeting of experts in order to assist the companies in undertaking the necessary studies.

In 2000, the three proprietary medicinal products UMATROPE, GENOTONORM and NORDITROPIN were listed (moderate AB and IAB III).

### 8.3. New clinical trials of efficacy submitted by the companies

In this request for renewed listing, the firms submitted new clinical studies and meta-analyses of the efficacy of rh-GH in adults. These are presented firm by firm in Appendix 2.

Three randomised, controlled, open-label studies were conducted in small groups of patients passing from childhood to adulthood:

- Conway\(^{14}\) showed a 6.0% increase in BMD of the spine in 160 young adults after 2 years of treatment with rh-GH compared to 2.0% in an untreated group (95% CI 1.5 - 5.5; \(p < 0.001\)).
- In 2004, Attanasio\(^{15}\) compared two doses of rh-GH (0.025 and 0.0125 mg/kg/day) over 2 years with a control group in a total of 149 patients. He showed an increase in lean body weight of 5.1 kg ± 3.9 (\(p < 0.001\)) and 5.2 kg ± 4.4 (\(p < 0.001\)) with these respective doses compared to the control group and a parallel decrease in fat weight of 1.6 kg ± 5.8 (\(p = 0.029\)) and 1.1 kg ± 4.0 (\(p = 0.029\)), respectively, with no difference between the two doses.
- In 2005, Attanasio\(^{16}\) monitored the quality of life (QLS-H scale) of three groups (two groups treated with 0.025 and 0.0125 mg/kg/day, respectively and one control group). In total, 66 patients were included. There was no significant difference between the treatment groups and the control group.

Two meta-analyses investigated muscle strength and were unable to demonstrate any effect:

- The meta-analysis by Rubeck\(^{17}\) investigated muscular effects of rh-GH treatment. Fifteen clinical trials were identified, with 306 patients treated for between 3 and 12 months. Aerobic exercise capacity increased by 8.9% ± 0.8 (\(p < 0.001\)). Muscle strength did not increase significantly. Muscle weight increased by 7.1% ± 1.6 (\(p < 0.001\)).
- The meta-analysis by Widdowson\(^{18}\) investigated the effect of rh-GH on muscle strength in adult patients with GH deficiency. Eight studies were identified, with a total of 231 patients, who received rh-GH for a mean period of 6.7 months. The results did not show any benefits of rh-GH treatment with respect to muscle strength.

Two non-comparative studies on small groups were submitted by the companies. They concern the efficacy of rh-GH on metabolic and bone parameters in adults as well as on the fat/lean mass distribution (Van der Klauuw\(^{23}\), Bravenbauer\(^{27}\)). However, the methodological characteristics (primarily the absence of comparison) of these studies do not enable significant and relevant results to be demonstrated.

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\(^{15}\) Attanasio et al. Continued growth hormone (GH) treatment after final height is necessary to complete somatic development in childhood-onset GH-deficient patients. J Clin Endocrinol Metab 2004; 89: 4857-62.


8.4. Other data from the literature on morbidity/mortality endpoints

In 2004, a French meta-analysis published by P. Maison et al.\textsuperscript{19} showed that adults treated with rh-GH had significant decreases in LDL-cholesterol (-0.5 mmol/l), total cholesterol (-0.3 mmol/l), diastolic blood pressure (-1.8 mmHg), fat weight (-3.1 kg) and significant increases in fasting blood glucose, lean body weight (+2.7 kg) and blood insulin (+8.7 pmol/l). It is not however possible to evaluate the effect on overall cardiovascular risk linked to changes in intermediate risk factors, which vary in opposing directions.

In 2004, Svensson\textsuperscript{20} compared the results of two studies and made an indirect comparison between a deficient adult population treated with rh-GH and one not treated with rh-GH. The first study, conducted in Sweden, investigated cardiovascular and cancer mortality and morbidity in a retrospective cohort of 1411 adults with a mean age of 57 years, with a pituitary deficiency not substituted with rh-GH, compared to those of a normal population. This population showed an excess all-cause mortality (RR = 3.80, 95% CI: [2.93 - 3.83]), excess myocardial infarction (RR = 1.40 95% CI: [1.10 - 1.75]), excess stroke (RR = 2.74 95% CI: [1.71 - 3.02]) and excess malignant tumours (RR = 1.50 95% CI: [1.16 - 1.91]) compared to the general population. The second study was of a prospective cohort of 289 patients, mean age 46 years, with a pituitary deficiency treated with rh-GH for 5 years. No differences were demonstrated between the treated patients and the general population with respect to mortality [RR = 0.84 (95% CI: 0.36 - 1.66)] and the occurrence of malignant tumours [RR = 0.88 (95% CI: 0.35 - 1.80)]. The incidence of myocardial infarction was lower in the treated patients than in the reference population, however there were only two such events.

The indirect comparison of these two results shows an excess mortality in untreated deficient patients, which is not found in the treated patients. However, since it is based on two studies with different designs, the comparison can be nothing more than indicative.

8.5. Additional post-marketing studies

8.5.1. Context

In 2000, the Transparency Committee made a request to all the companies concerned that “longitudinal monitoring is set up for all adult patients on initiation of treatment”. In response to this request, the companies set up observational cohort studies of patients treated with growth hormone, who were monitored for 5 years. Patients were included in these studies from 2003 for the oldest preparations (GENOTONORM, NORDITROPIN, UMATROPE and SAIZEN) and from 2005 for NUTROPINAQ. No communal study was set up, but different studies were conducted by each of the companies on their product in particular, with the record book used being for the most part communal to all the companies. Moreover, the analysis was performed in an identical manner. It should be noted that these studies did not measure the quality of life of treated patients.

Preliminary results have been received for five growth hormone preparations (NORDITROPIN, GENOTONORM, SAIZEN, UMATROPE and NUTROPINAQ). In the case of OMNITROPE, the study protocol was validated in 2009 and, as of 13/02/2012, two patients have been enrolled (of the 100 planned). Thus there are as yet no results for this proprietary medicinal product. The results presented below therefore apply to five of the six products which have an indication in adults (NORDITROPIN, GENOTONORM, SAIZEN, UMATROPE and NUTROPINAQ). Only baseline results are currently available for NUTROPINAQ; follow-up data are also available for the other four proprietary medicinal products (NORDITROPIN, GENOTONORM, SAIZEN, UMATROPE).


\textsuperscript{20} Svensson J. Malignant disease and cardiovascular morbidity in hypopituitary adults with or without growth hormone replacement therapy. J Clin Endocrinol Metab. 2004; 89: 3306-12.
The prescription of rh-GH is covered by a prescription guide (fiche d’information thérapeutique; FIT).

8.5.2. Characteristics of the results

The results submitted by the companies are interim results. No pooled analysis of all adult patients treated with rh-GH is available for these studies. However, since a large proportion of the collected data is communal and the manner of analysis identical, the results are presented in a grouped fashion.

The following points must be emphasized before the results can be read:
- the exhaustiveness of the centres and patients enrolled in these studies is not disputed;
- in some studies, discontinuation of treatment was not reported;
- we do not have precise information on the number of patients lost to follow-up at the various follow-up times;
- missing data frequently occur during follow-up.
- The descriptions of enrolled patients in some consecutive interim reports differ from each other, which brings into question the quality control performed on the collected data.

Overall, extreme caution is required when considering these results.

8.5.3. Main characteristics of patients at the time of diagnosis

The mean age at which patients were diagnosed with GH deficiency is approximately 32 years, except in the case of SAIZEN, where the patients are younger (19 years on average). In these studies, the deficiency manifested in the majority of patients during adulthood (59% to 83% of cases), except in the case of SAIZEN, where the deficiency manifested during childhood in 56% of cases.

In the majority of cases, the pituitary disease was of secondary aetiology (in 71% to 88% of cases); the most frequent cause was a tumour (59% to 80% of cases), more specifically an adenoma (44% to 72% of cases).

Depending on the study, at least one stimulation test was conducted and validated in 30% to 55% of patients.

At diagnosis, the IGF-1 level was low in 43% to 60% of patients, normal in 17% to 60% and not determined in approximately a quarter of cases.

In 41% to 83% of cases, the diagnosis of GH deficiency was made and documented, while in the remaining cases the diagnosis had most commonly been made during childhood or adulthood, but was not documented.

Most of the patients enrolled in these studies had other hormonal deficiencies (90% to 96% of cases): deficiency of thyroid-stimulating hormone (78% to 85%), adrenocorticotrophic hormone (67% to 81%), luteinising hormone (80% to 84%) and, less commonly, antidiuretic hormone (24% to 29%). In almost 85% of cases, the patients were receiving hormonal substitution treatment to treat these deficiencies.

Most commonly, patients had three combined deficiencies (between 39% and 46% of cases).

8.5.4. Main characteristics of patients and their treatment at baseline

The mean age of patients at baseline was between 32 and 42 years. The gender ratio varied from 0.83 to 1. The BMI was between 26.4 (± 5.8) and 27.9 (± 5.9) and the waist/hip ratio between 0.90 and 0.92.

The mean daily dose of rh-GH prescribed was between 0.30 and 0.38 mg/day and the number of injections prescribed per week was 7 in 88% to 97% of cases, as recommended in the FIT.

At baseline, the IGF-1 level was low in 7% to 50% of patients, normal in 22% to 75%, elevated in 2% to 7% and not determined in 5% to 43%.
8.5.5. Main results of patient follow-up

Depending on the study, the follow-up rate of patients ranges from 49% to 78% at 1 year, from 42% to 69% at 2 years, from 25% to 58% at 3 years and less than 50% in all cases at 4 years. Somewhat less than one third of patients have been followed-up for at least 3 years. The mean duration of follow-up is from 1.5 to 2.2 years, depending on the proprietary medicinal product in question. Furthermore, the results of patient follow-up are still too fragmentary and should be interpreted with caution.

With respect to clinical and biological monitoring parameters (BMI, waist/hip ratio, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and blood glucose), their values appear to be relatively stable over time during the first 3 years of monitoring.

It can be seen that antidiabetic, antihypertensive and hypolipidaemic treatments appear to be co-prescribed relatively frequently during the first 3 years of monitoring.

Permanent discontinuation of treatment has occurred in 2.5% to 13.2% of patients in the course of follow-up. The reasons for discontinuation were problems associated with the injection in a quarter of the cases, adverse events in another quarter and inefficacy in the third quarter, while another (undefined) reason was cited for the final quarter.

According to the study, adverse events occurred in between 28% and 58% of patients and were related to the treatment in 13% to 27% of cases. SAE occurred in 6% to 47% of patients depending on the study.

Overall, the results of these post-marketing studies are of too low methodological quality to be able to be taken into account. In particular, there is no guarantee of the exhaustiveness of inclusion of centres and patients nor is there any guarantee of the data quality, and the patients have been monitored for a too short period.

Nevertheless, the preliminary results for clinical and biological parameters do not appear to show any impact on the morbidity of treated patients, all the more so since other cardiovascular treatments are often co-prescribed.

With respect to conditions of use, in the majority of cases, the treatment appears to be used in accordance with the recommendations of the FIT (indications, dosage and frequency of injections).

8.6. Clinical Practice Guidelines

The companies used the 2011 guidelines of the US Endocrine Society concerning the evaluation and treatment of adults with growth hormone deficiency. However, all except one of the five experts participating in these guidelines declared a relationship with one or more companies marketing growth hormone.

In particular, the Endocrine Society recommends:

- that patients with growth hormone deficiency acquired in childhood should be retested at adulthood when they are candidates for continuation of treatment (high level of evidence).
- Treatment with rh-GH in adult patients with GH deficiency provides significant clinical benefits in terms of body composition and capacity for physical exercise (moderate level of evidence).
- Treatment with rh-GH in adult patients with GH deficiency provides significant clinical benefits in terms of bone integrity (low level of evidence).
- In the case of GH deficiency persisting after growth is completed, it is recommended to continue rh-GH treatment after the final height is reached so as to achieve full maturation of bones and muscles during the transition period (low level of evidence).
- Although mortality is increased in patients with hypopituitarism and the GH deficiency is involved in this mortality, treatment with rh-GH has not yet been demonstrated to improve survival (very low level of evidence).
- Treatment of growth hormone deficiency in adults with rh-GH increases the quality of life of the majority of patients (low level of evidence).
- It is recommended that treatment with rh-GH should be contraindicated when an actively malignant tumour is present (very low level of evidence).
- It is recommended to adjust antidiabetic treatment in diabetic patients treated with rh-GH (moderate level of evidence).
- It is suggested that thyroid and adrenal functions should be monitored during treatment with rh-GH (low level of evidence).

In 2003, NICE published a report, which was updated in 2006,\textsuperscript{21} evaluating rh-GH in deficient adults. The conclusions are as follows:

Recombinant growth hormone should only be given to an adult with a deficiency, who meets the following three criteria:
- He/she has a severe deficiency, defined as a GH peak of < 3 ng/ml during an insulin tolerance test or a GH threshold validated in a crosswise manner by means of an equivalent test.
- The quality of life has changed perceptibly, as shown by a score of at least 11 on a questionnaire specific for GH deficiency (QoL-AGHDA).
- He/she is already receiving the other pituitary replacement treatments required.

With respect to efficacy, the NICE evaluation is based on 17 randomised clinical trials and 9 post-marketing studies evaluating quality of life. Twenty-three quality of life scales were used. The most commonly used scale (in 10 trials) was the NHP.\textsuperscript{22} The QoL-AGHDA scale\textsuperscript{23} was used in two trials.

In 2010, Malaysia\textsuperscript{24} published guidelines stating that growth hormone should only be used in adult patients if they have clinical symptoms of GH deficiency, a proven alteration in quality of life and a confirmed GH deficiency.

8.7. Tolerance
The data from the SPC and PSUR, presented in the previous section, concerning deficiency in children apply to all patients receiving growth hormone, regardless of age.

The SPC states that in adults with growth hormone deficiency, oedema, myalgia, arthralgia and joint problems were reported at the start of treatment and were mostly transient.
The incidence of adverse effects is lower in adults treated with growth hormone, who have had growth hormone deficiency since childhood, than in those who acquired deficiency as adults.

Several studies on the safety of rh-GH in adults were submitted by the companies:
- In one follow-up study in adults,\textsuperscript{25} the most commonly notified adverse effects, in order of incidence were: arthralgia, myalgia, headache, depression, asthenia and paraesthesia.
Over the longer term, there are no specific data on cancer risk in adults.

- One recent cohort study, conducted by Attanasio\textsuperscript{29} in 2011, and supplied in the dossier of several companies, investigates the risk of an increase in diabetes.
This is a study conducted by Lilly, which included 6672 patients in Europe and the United States and formed part of the HypoCCS follow-up in adults established by the firm. The patients had a mean age of 45 years and were not diabetic at baseline. The overall incidence was 2.1/1000

\textsuperscript{21} National Institute for Clinical Excellence. Human growth hormone (somatropin) in adults with growth hormone deficiency. August 2003, Review date: July 2006. www.nice.org.uk
\textsuperscript{22} NHP: Nottingham Health. Scale validated in France in the general population.
\textsuperscript{23} Quality of life scale from 0 to 25, specific for growth hormone deficiency.
\textsuperscript{25} SAIZEN, MEGHA study, interim data submitted by the company in 2012.
patient-years (95% CI: [8.4 to 10.9]), and in Europe the incidence was 7.0/1000 patient-years (95% CI: [5.6 to 8.3]), which is comparable to that of the reference population. The study did not find any correlation between the dose of rh-GH and the incidence of diabetes.

- Two case-control studies (Mackenzie and Olsson) had the objective of evaluating the effect of treatment with rh-GH on the incidence of tumour recurrence or secondary tumours following cranial irradiation. The duration of follow-up was 14.5 years and 10 years in the first study and the results showed a risk of tumour recurrence or secondary tumours of 10% in the two groups. In the second study, the rate of progression-free survival at 10 years was 74% in treated patients and 70% in untreated patients, with the difference not being significant.

8.8. Conclusion on data in deficient adults

Growth hormone deficiency in adults results in asthenia and an increased cardiovascular risk. The initial data on the efficacy of rh-GH in deficient adults relate solely to intermediate endpoints: distribution of fat/lean body weight, bone mineral density, quality of life/well being. The improvement in these parameters was modest. New data relating to morbidity and mortality are awaited.

The new studies submitted by the companies are of poor methodological quality, but they confirm these modest results in the intermediate endpoints. Data from the literature and those supplied by the companies do not enable an objective assessment of the effect of rh-GH on mortality or on serious cardiovascular or tumour events.

The most common adverse effects over the short term are identical to those observed in children. Over the long term, no epidemiological study raises the suspicion of cancer risk in adults. There is a slight increase in fasting blood glucose and in blood insulin, which should be set against the moderate improvement in cardiovascular risk factors.

The results of the follow-up studies requested in 2002 by the Transparency Committee are still partial, of low quality, and do not include quality of life data. The interim results that are available do not show any impact of treatment on the morbidity of treated patients.

NICE recommends that the use of growth hormone in adult deficiency should be limited to patients with a severe deficiency, confirmed by laboratory tests, whose quality of life is affected and who are already receiving the other substitution treatments they require for pituitary deficiencies.

In summary, almost 15 years after the initial evaluation, the available data on the efficacy of rh-GH in adult deficiency remain of mediocre quality and doubts concerning its long-term efficacy on morbidity and mortality have not been dispelled.
9 RE-EVALUATION OF ACTUAL BENEFIT

9.1. AB in childhood deficiency
Growth hormone deficiency in children is a disease of varying origin (idiopathic or secondary to pituitary disease), which can be isolated or associated with other pituitary deficiencies. It leads to short size and variable symptoms, as weight gain, metabolic risk, asthenia and deterioration in the quality of life.

These proprietary medicinal products are intended for use as part of symptomatic therapy.

The efficacy/adverse effects ratio for these proprietary medicinal products in this indication is important.

These medicinal products are first-line therapies.

There is no alternative medicinal product to somatropin that has an effect on height.

Public health benefit:
Growth retardation in children associated with growth hormone deficiency represents a small burden to public health on account of the limited number of patients affected.
On account of the social seriousness of this rare disease, improvement of its management is a public health priority.
In view of the available data, the impact on morbidity (gain in height) is moderate. In the absence of available data, the impact on the quality of life cannot be quantified.
Consequently, these products present a small benefit to public health in this indication.

The actual benefit of SAIZEN in children with GH deficiency remains substantial.

9.2. AB in adult deficiency
Growth hormone deficiency in adults is a chronic disease of varied origin, which can result in deterioration of quality of life and cardiovascular complications.

The efficacy/safety ratio in this indication is moderate.

There is no alternative treatment for growth hormone deficiency.

There is no alternative medicinal product to somatropin.

Public health benefit:
Severe growth hormone deficiency in adults is a low public health burden because of the limited number of patients concerned.
Improvement of the management of this deficiency is not a public health priority.
In view of the low level of evidence of the submitted studies, the impact of these proprietary medicinal products on morbidity and quality of life of treated patients has not been determined.
In consequence, the benefit to public health provided by growth hormones in this indication in adults cannot be quantified.

The actual benefit of SAIZEN in adults with GH deficiency remains moderate.
9.3. AB in growth retardation associated with Turner Syndrome

Turner syndrome of genetic origin is a rare disease combining short stature, dysmorphia, pubertal development and fertility problems, malformation of certain organs (heart, vessels and kidneys, in particular) and an increase in cardiovascular mortality.

This proprietary medicinal product forms part of the curative therapy for short stature used in the overall management of the disease.

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

There is a safety issue, suggesting excess mortality in adults who used growth hormone in childhood. Additional studies are necessary to draw conclusions.

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

There is no alternative medicinal product to somatropin with an effect on height.

Public health benefit:
Childhood growth failure linked to Turner syndrome represents a low public health burden due to the limited number of patients concerned.
Since this disorder is a rare disease, its management is a public health need (Second National Plan for Rare Diseases 2010-2014).
This disease requires comprehensive, multi-disciplinary management; growth hormone treatment is only one aspect.
In view of the available data, the impact of growth hormone on the final height of children is, at best, moderate. Psychologically and socially, and in regard to quality of life, this impact has not been established.
Furthermore, a negative impact cannot be ruled out, especially because of questions concerning the long-term risk of occurrence of cancer, diabetes and cardiovascular diseases.
In addition, the transferability of trial data is not certain, especially because of compliance problems linked to the need for daily injections for a long period.
Consequently, growth hormone does not provide a public health benefit in the treatment of growth failure in girls with Turner syndrome confirmed by chromosomal analysis.

Taking into account all of the data examined, the actual benefit of SAIZEN in Turner syndrome remains substantial.

9.4. AB in growth retardation associated with chronic renal impairment

Chronic renal impairment in children is a rare and serious disease the outcome of which varies according to aetiology and sometimes leads to death of the child. Short stature is only one element of this disease; it may contribute to a marked deterioration in quality of life.

This proprietary medicinal product forms part of the curative therapy for short stature used in the overall management of the disease.

The efficacy of growth hormone on height in chronic renal impairment has been demonstrated at the end of the trial and confirmed in other studies on other height parameters. Observational studies confirm the efficacy observed in clinical trials. For the short study period before transplant, the height gain is small, but it contributes to the necessary management of the disorder.
There is a safety issue, suggesting excess mortality in adults who used growth hormone in childhood. Additional studies are necessary to draw conclusions.
The efficacy/adverse effects ratio for this medicinal product in this indication is modest.

There is no alternative medicinal product to somatropin with an effect on height.

Public health benefit:
Childhood growth failure linked to chronic renal impairment represents a low public health burden due to the limited number of patients concerned.
Since this disorder is a rare disease, its management is a public health need (Second National Plan for Rare Diseases 2010-2014).
This disease requires comprehensive, multi-disciplinary management; growth hormone treatment is only one aspect.
In view of the available data, the impact of growth hormone on the height of children is, at best, moderate. The impact of treatment on adult height has not been established. Psychologically and socially, and in regard to quality of life, this impact has not been established.
Furthermore, a negative impact cannot be ruled out, especially because of questions concerning the long-term risk of cancer, diabetes and cardiovascular diseases.
In addition, the transferability of trial data is not certain, especially because of compliance problems linked to the need for daily injections for a fairly long period.
Consequently, growth hormone does not provide a public health benefit in the treatment of growth failure linked to chronic renal impairment.

Taking into account all of the data examined, the actual benefit of SAIZEN in chronic renal impairment remains substantial.

9.5. AB in growth failure in children born small for gestational age
Growth failure in children born small for gestational age (SGA), who did not have catch-up growth at age 4, is characterised by isolated short stature of unidentified origin.

This proprietary medicinal product forms part of the curative therapy for short stature.

The efficacy of growth hormone on adult height in SGA has been demonstrated in one study and confirmed in other studies on other height parameters. The height gain is small. Observational studies confirm the weak efficacy observed in clinical trials.
There is a safety issue, suggesting excess mortality in adults who used growth hormone in childhood. Additional studies are necessary to draw conclusions.

The efficacy/adverse effects ratio of this product is low in this indication.

There is no alternative medicinal product to somatropin with an effect on height.

Public health benefit:
Growth failure in children born small for gestational age who did not have catch-up growth at age 4 or more represents a low public health burden due to the limited number of patients concerned.
Since this disorder is a rare disease, its management is a public health need (Second National Plan for Rare Diseases 2010-2014).
In view of the available data, the impact of growth hormone on the final height of children is, at best, weak. The impact of treatment on adult height has not been established. Psychologically and socially, and in regard to quality of life, this impact has not been established.
Furthermore, a negative impact cannot be ruled out, especially because of questions concerning the long-term risk of cancer, diabetes and cardiovascular diseases.
In addition, the transferability of trial data is not certain, especially because of compliance problems linked to the need for daily injections for a long period.
Consequently, growth hormone does not provide a public health benefit in the treatment of growth retardation in children born small for gestational age with a birth weight and/or length below -2 SD, who failed to show catch-up growth (growth velocity < 0 SD during the last year) by 4 years of age or later.

The actual benefit of SAIZEN in children born small for gestational age with a birth weight and/or length < -2 SD, who have failed to show catch-up growth (growth velocity < 0 SD during the last year) by 4 years of age or later and whose growth retardation (current height) is below or equal to -3 SD and the adjusted parental height < -1 SD 

**remains low.**

9.6. **Transparency Committee recommendations**

The Transparency Committee recommends continued inclusion of SAIZEN on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in its indications.

The Transparency Committee maintains its recommendation for reimbursement of growth hormone for children with growth retardation (current height) less than or equal to -3 SD and parental adjusted height < -1 SD) in the indication of children born small for gestational age with a birth length below -2 SD, who failed to show catch-up growth (growth velocity < 0 SD during the last year) by 4 years of age or later.

9.6.1. **Packaging:** Appropriate for the prescription conditions in the MA

9.6.2. **Reimbursement rate:** 100 %

9.6.3. **Exception status:** rh-GH proprietary medicinal products continue to have exception status.
APPENDIX 1

Indication of childhood deficiency

DATA SUBMITTED BY EACH OF THE COMPANIES IN THE DOSSIER FOR THE REQUEST FOR RENEWAL OF INCLUSION

1. GENOTONORM/PFIZER

- **KIGS cohort (Kabi International Growth Study)**: international database established by PFIZER in 1987 with the objective of obtaining data on long-term efficacy and safety of biosynthetic growth hormone. According to data published by Ranke, in 2007 almost 60,000 patients in all indications combined had been included.
  * Of these, 28,088 children had an idiopathic deficiency and 7137 patients had an organic deficiency. When the deficiency was organic, it was acquired (primarily pituitary tumours) in 67% of cases and congenital in 33%.
  * The mean dose administered was from 0.026 mg/kg/day in girls to 0.029 mg/kg/day in boys (in accordance with the dosage stated in the MA).
  * The results on height were expressed as a gain in height (before/after comparison) from the baseline height to the height attained with treatment. In idiopathic deficiency, the gain in height at 3 years was +1.5 SDS (4802 patients), the gain in height for adult height was between +1.7 SDS (isolated deficiency, 1221 patients) and +2.5 SDS (multiple deficiencies, 686 patients). In cases of acquired organic deficiency (383 patients), the gain in height at adult age varied between +1.7 SDS and -0.1 SDS, depending on the cause of the deficiency. In cases of malignant tumours, there was no gain in height SDS at adult age compared to the baseline height (no change in the growth curve).

These results represent the limits of an observational and non-comparative cohort, with large numbers lost to follow-up, which will give overestimated results.

- The case-control study from Salerno, which compared a group of 30 children of small stature and with growth hormone deficiency, who were treated daily with rh-GH 0.030 mg/kg/day, with 30 untreated children of normal height. The aim of this study was to compare cardiovascular risk factors between the two groups. The results at two years show the rh-GH group to have an improvement in ventricular mass index and lipid profile (total cholesterol: 3.5 mmol/l ± 0.1 in the treated group vs. 4.2 mmol/l ± 0.1 in the untreated group, p < 0.0001), but a decrease in insulin sensitivity (increase in blood insulin in the treated group with no difference in blood glucose between the two groups).

2. NORDITROPIN/NOVO NORDISK PHARMACEUTIQUE SAS

With respect to children with a deficiency, the company submitted only one dosage study, which presents growth rate over 1 year. This study is of no relevance, due to its short duration of treatment and its design, and is not presented in the opinion.

3. UMATROPE/LILLY France

In the indication of children with a deficiency, only new studies relating to adult height are described in this opinion. These are two observational studies, which confirm the efficacy of growth hormone on adult height in this indication. In addition, one study comparing growth velocity over 1 year with UMATROPE and with a growth hormone that is not marketed in France, has not been cited.
- The retrospective Canadian cohort study by Rachmiel\textsuperscript{4} of 96 children treated for GH deficiency with UMATROPE, NUTROPINAQ or SAIZEN at a fixed dosage of 0.03 mg/kg/day aimed to evaluate adult height following treatment. The deficiency was idiopathic in 65% of cases. The mean duration of treatment was 11.9 years. The results showed that 84% of children reached a normal adult height, which was greater than -2 SDS (-1.04 ± 1.00 SDS), with a gain in height of +1.8 ± 1.2 SDS. A steady increase in height SDS was observed.

- Results as of September 2008 of the GENESIS post-marketing study conducted by the firm (not published). This is a non-comparative observational study in 9697 children treated with UMATROPE for growth hormone deficiency, with the children being monitored until treatment was discontinued. The results of the French cohort of patients with growth hormone deficiency initially showed the mean age at start of treatment to be 9-10 years, with a short baseline stature of the order of -2.50 to -2.40 SDS. The adult height is known for 1439 patients (all countries, approximately 15% of patients), including 127 French patients. The mean duration of treatment was 3 years for patients in the French cohort and more than 4 years for all patients in the study. The results for mean adult height (all countries) show it to be within the normal range of -1.02 ± 1.13 SDS, with a mean gain in height from baseline of 1.44 ± 1.18 SDS.

4. ZOMACTON/FERRING SAS

- One retrospective French cohort study from 2009\textsuperscript{3} included children with isolated or combined GH deficiency, who were treated from before the age of 1 year and for more than 15 years. All children on the France Hypophyse register meeting this criteria were included if their growth profiles were known (this being 44/59 patients). At the time of diagnosis, the height was -2.6 SDS ± 1.9. The maximum catching up took place during the first 3 years, when the children made up approximately 3/5 of their height deficiency. At a mean age of 22 years, the mean height was -0.3 SDS ± 1.3, which was almost equivalent to the expected height of -0.4 SDS ± 0.8.

- One randomised controlled study\textsuperscript{7} compared the administration of two doses of growth hormone during puberty. The 49 children who were enrolled, were divided into two groups to receive either 0.7 or 1.4 mg/m\textsuperscript{2}/day. Prior to randomisation, they had all been treated for at least one year with 0.7 mg/m\textsuperscript{2}/day of rh-GH. The total duration of treatment with rh-GH was more than 5 years for all patients. The results for final gain in height SDS compared to expected height did not differ between the groups: +1.1 SDS in the first group and +1.2 SDS in the second group, p = 0.81. In conclusion, increasing the dosage during puberty does not have a significant effect on the final height of patients with GH deficiency.

- The company also submitted the study by Rachmiel\textsuperscript{4} (see above).

5. NUTROPINAQ/IPSEN PHARMA

Two post-marketing studies were set up by the company in order to collect data on prescription and efficacy in patients receiving NUTROPINAQ (NUTROPIN in USA).


- The mean age at inclusion for children with idiopathic deficiencies was 11.4, while for those with organic deficiencies it was 9.0 years.

- Height at inclusion was -2.2 ± 1.0 SDS for those with idiopathic deficiencies and -2.0 ± 1.6 SDS for those with organic deficiencies.

- The mean doses of growth hormone used were 0.316 ± 0.081 mg/kg/day for those with idiopathic deficiencies and 0.282 ± 0.105 mg/kg/day for those with organic deficiencies.
Results: For idiopathic deficiencies, the gain in height was $0.7 \pm 0.6$ SDS (1001 children) at 1 year and $0.4 \pm 0.4$ SDS (336 children) at 2 years. For organic deficiencies, the gain in height was $0.9 \pm 1.1$ SDS (300 children) at 1 year and $0.4 \pm 0.7$ SDS (138 children) at 2 years.

The iNGCS European study included 440 children. The European data show results similar to those of the North American follow-up study:

- The mean age at inclusion for children with idiopathic deficiencies was 10.6, while for those with organic deficiencies it was 10.0 years.
- Height at inclusion was $-2.4 \pm 0.9$ SDS for those with idiopathic deficiencies and $-2.2 \pm 1.2$ SDS for those with organic deficiencies.
- The mean doses of growth hormone used were $0.216 \pm 0.044$ mg/kg/day for those with idiopathic deficiencies and $0.212 \pm 0.047$ mg/kg/day for those with organic deficiencies.

Results: For idiopathic deficiencies, the gain in height was $0.7 \pm 0.4$ (85 children) at 1 year and $0.4 \pm 0.4$ (336 children) at 2 years. For organic deficiencies, the gain in height was $0.7 \pm 0.4$ SDS (23 children) at 1 year.

In conclusion: The results observed are of the same order of magnitude in the two studies and smaller than the results observed in the initial efficacy studies, for which inclusion criteria were stricter (+1.1 SDS in 1 year in study L0368g and +2.2 SDS in 4 years in study 87070). Furthermore, the numbers lost to follow-up during the first year and the short duration of follow-up do not enable these results to be confirmed with respect to adult height.

6. OMNITROPE/SANDOZ SAS

Four studies were included in the dossier: Only 3 new studies, relating to a period greater than or equal to 4 years, are presented:

- Study by Romer, published in 2009. This is an open-label study in deficient patients, which followed on from studies EP2K-99-PhIII and EP2K-00-PhIIIFo. These latter studies, which have already been reviewed by the Transparency Committee during the listing of OMNITROPE, showed the non-inferiority of OMNITROPE compared to GENOTONORM. The overall period of treatment was 7 years. The number of children treated over 7 years in the two groups was 49 and their mean age at baseline was 7.6 years. The mean baseline height was $-3.06 \pm 0.80$ SDS. At the end of the trial (after 7 years), the mean height was $-0.78$ SDS in the group treated with OMNITROPE and $-1.01$ SDS in the GENOTONORM group. The mean final projected height was 172.5 ± 6.4 cm for the boys and 160.0 ± 5.7 cm for the girls.

- Study EP2K-00-PhIIIf-E was not published: This is an open-label non-comparative study in 70 deficient children treated for 4 years with OMNITROPE. The mean age at baseline was $8.7 \pm 2.4$ years. Only 31 children were monitored for 4 years. The mean baseline height was 118.72 ± 12.52 cm, i.e. $-2.24 \pm 0.40$ SDS, and the mean height at the end of the study was 148.8 ± 12.0 cm, i.e. $0.91 \pm 0.86$ SDS.

- Study EP2K-02-PhIIif-Lyo was not published: This is an open-label non-comparative study in 51 deficient children treated for 4 years with OMNITROPE. The mean age at baseline was 7.6 ± 2.6 years. The mean baseline height was 111.9 ± 15.5 cm, i.e. $-3.21 \pm 1.00$ SDS. The mean height at the end of the study was 142.84 ± 14.02 cm, i.e. $-1.11 \pm 1.03$ SDS. Two other open-label clinical trials with OMNITROPE over 4 years confirm these results.

7. SAIZEN/MERCK SERONO

No new data likely to change the benefit/risk ratio in deficient children.
APPENDIX 2

INDICATION: ADULT DEFICIENCY

DATA SUBMITTED BY EACH OF THE COMPANIES
IN THE DOSSIER FOR THE REQUEST FOR RENEWAL OF INCLUSION

Only the meta-analyses and randomised clinical trials on rh-GH efficacy with sufficiently large numbers (>30) and using relevant clinical endpoints are presented below. Furthermore, with respect to safety, only large cohort monitoring studies based on a comparison with an untreated population are included.

Post-marketing monitoring studies are only presented in the relevant section.

In August 2012, firms marketing growth hormone were requested to update data for adult deficiency. These additional data are described where appropriate after the description of the initial dossier.

1. GENOTONORM/PFIZER

The randomised open-label study from Conway in 2009 evaluated the effect of 2 years of treatment with rh-GH on mean bone mineral density (BMD) in 160 young adults aged 18 to 25 years with growth hormone deficiency acquired in childhood. They were randomised into two groups of treated (109) and untreated (51) patients. The dose administered was progressively increased, starting at 0.2 mg/day and increasing after 1 month and 3 months up to 1.0 mg/day in men and 1.4 mg/day in women.

BMD was evaluated at baseline and then after 6, 9, 12, 18 and 24 months. A greater improvement in BMD was seen after 2 years in the lumbar vertebrae of the treated group than of the untreated group: the change in BMD from baseline to 24 months in the treated group versus the untreated group was 0.05 g/cm² vs. 0.02 g/cm², and the difference between the two groups was estimated at 3.5% of the baseline BMD (95% CI: 1.5 – 5.5; p < 0.001).

As of August 2012, no other clinical trial on the efficacy of rh-GH had been submitted.

2. NORDITROPIN/NOVO NORDISK PHARMACEUTIQUE SAS

The company presented two published studies on metabolic, anthropometric and bone parameters:
- the study by Van der Klauuw published in 2006, which evaluated the long-term benefit of rh-GH treatment on anthropometric and metabolic parameters in deficient adult patients. The study lasted 7 years and included 88 patients with severe deficiency with an rh-GH peak of 3.3 µg/l. The patients were treated with rh-GH at an initial dose of 0.2 mg/kg/day, which was subsequently adjusted so as to obtain a level of circulating IGF-1 between 0 and 2 SDS. At the end of the study, the steady-state dose was 0.5 mg/kg/day. Results for the 67 patients, who completed the study were as follows: BMI increased significantly from 25.5 ± 3.3 to 27.1 kg/m² ± 3.9 (p < 0.001), the effect on blood pressure was not significant, an increase in blood glucose from 4.4 mmol/l ± 0.7 to 5.0 ± 1.0 (p < 0.001) was observed throughout the monitoring, LDL cholesterol decreased significantly from 4.73 mmol/l ± 1.1 mmol/l to 3.5 ± 0.9 mmol/l (p < 0.001) after patients treated with a hypolidaemic agent were excluded.

The study from Bravenbauer published in 2005 showed the effect of rh-GH after 5 years on bone metabolism in the indication of growth hormone deficiency in adults. The study included 50 adult men, with a GH peak of < 7 µg/l. The rh-GH dosage varied from year to year from 0.63 to 0.43 mg/m²/day, being adjusted according to IGF-1 level during the final 3 years. The results show an increase in the bone density and mineral content, particularly in the cortical bone. After 5 years, the most significant change from baseline was in the bone mineral density (BMD) of the trochanter: 0.74 ± 0.14 before treatment and 0.83 ± 0.14 after 5 years of treatment.

In August 2012, the company also submitted the study published by Conway.¹⁴

3. **UMATROPE/LILLY France**

Two studies have been published concerning deficiency during the transition period from childhood to adulthood.

This period generally lasts from the time adult height is attained until the age of 25 years. Growth hormone plays a part in body composition and the attainment of adult muscular mass as well as in the attainment of the peak of bone mass.

**Attanasio 2004**¹⁵

This is a randomised, controlled, open-label study over 2 years, which included deficient patients treated with rh-GH in childhood, who had completed their treatment with rh-GH after reaching their final height: 58 patients received 0.025 mg/kg/day, 59 received 0.0125 mg/kg/day and 32 patients did not receive rh-GH. The endpoints were the evolution of fat and lean body weight. After 2 years, the results showed an increase in lean body weight in the two treatment groups compared to the control group: +5.1 ± 3.9 kg (p < 0.001) with 0.50 mg/kg/day and + 5.2 ± 4.4 kg (p < 0.001) with 0.025 mg/kg/day as well as a decrease in body fat in both groups: -1.6 ± 5.8 kg (p = 0.029) with 0.50 mg/kg/day and -1.1 ± 4.0 kg (p = 0.029) with 0.025 mg/kg/day.

**Attanasio 2005**¹⁶

This is a randomised, controlled, open-label study over 2 years on the quality of life of deficient patients treated with rh-GH in childhood, who had completed their treatment with rh-GH after reaching their final height: 25 patients received 0.025 mg/kg/day, 28 received 0.0125 mg/kg/day and 13 patients did not receive rh-GH. The endpoints were quality of life evaluated by means of the QLS-H scale²⁸ and 66 patients were enrolled. The results show a non-significant difference between the control group and the treatment groups at 1 year and 2 years.

In August 2012, the firm submitted a recent cohort study conducted by Attanasio in 2011 on the risk of an increase in diabetes. This is a study conducted by Lilly, which included 6672 patients in Europe and the United States and formed part of the HypoCCS follow-up in adults established by the firm. The patients were adults, with a mean age of 45 years, not diabetic at baseline and not having received rh-GH as adults yet. The prevalence of diabetes was 8.2% (95% CI: [7.6 to 8.9]). The overall incidence was 2.1/1000 patient-years (95% CI: [8.4 to 10.9]), and in Europe the incidence was 7.0/1000 patient-

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years (95% CI: [5.6 to 8.3]), which is comparable to that of the reference population. The study did not find any correlation between the dose of rh-GH and the incidence of diabetes.

4. **NUTROPINAQ/IPSEN PHARMA**

In August 2012, IPSEN conducted a literature search for clinical studies and meta-analyses of the efficacy and safety of somatotropin in the indications in the MA.

- The Attanasio study of 2011 described in the paragraph above investigated the incidence of diabetes in a cohort of patients treated with rh-GH.
- The study by Mackenzie had the objective of evaluating the effect of treatment with rh-GH on the incidence of tumour recurrence or secondary tumours detected by MRI following cranial irradiation. This is a matched-pair retrospective study. One hundred and ten (110) pairs of patients were formed. The median duration of follow-up was 14.5 years. The results showed a 10% risk of recurrence or secondary tumour in both groups. There was no significant difference between the groups.
- The case-control study by Olsson aimed to evaluate the effect of treatment with rh-GH on the incidence of tumour recurrence after radiotherapy of adenoma. One hundred and twenty-one (121) patients treated with rh-GH were paired with 114 untreated patients. The mean duration of follow-up was 10 ± 4 years. The results showed that the rate of progression-free survival at 10 years was 74% in treated patients and 70% in untreated patients, with the difference not being significant.
- The Rubeck meta-analysis investigated the effects of rh-GH treatment on aerobic exercise capacity, muscle strength and muscle mass. Fifteen clinical trials were identified, with 306 patients treated for between 3 and 12 months. Aerobic capacity increased by 8.9% ± 0.8% (p < 0.001). Muscle strength did not increase significantly. Muscle weight increased by 7.1% ± 1.6 (p < 0.001).
- The Widdowson meta-analysis investigated the effect of rh-GH on muscle strength in adult patients with GH deficiency. Eight studies were identified, with a total of 231 patients, who received rh-GH for a mean period of 6.7 months. The results did not show any benefits of rh-GH treatment with respect to muscle strength.

5. **OMNITROPE/SANDOZ SAS**

No study with OMNITROPE in adults has been submitted.

6. **SAIZEN/MERCK SERONO**

When submitting the dossier, the company did not provide any new data likely to change the benefit-risk relationship in deficient adults.

In August 2012, the company also submitted:

- The Rubeck meta-analysis, which investigated the effects of rh-GH on muscle (see above).
- The study by Conway (see above).

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