TRANSPARENCY COMMITTEE

OPINION

3 October 2012

Review of the dossier for proprietary medicinal products included for a 5-year period starting on 4 August 2005 (Official Gazette of 29 December 2006)

**ZOMACTON 10 mg/ml, powder and solvent for solution for injection in pre-filled syringe**
B/1 glass vial + 1 pre-filled syringe, 1 ml (CIP: 370 840-3)

**ZOMACTON 4 mg, powder and solvent for solution for injection in multidose container**
B/1 vial + 1 ampoule, 3.5 ml (CIP: 342 154-1)

These medicinal products can be administered either with a conventional syringe or with the ZOMAJET medical device.

Applicant: FERRING SAS

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, Reference Member State France)
ZOMACTON 4 mg: 26 February 1992
ZOMACTON 10 mg/ml: 16 June 2006

Reason for request: Renewal of inclusion on the list of proprietary medicinal products refundable by National Health Insurance.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Somatropin

1.2. Indications
“ZOMACTON is indicated for:
- the long-term treatment of children who have growth failure due to inadequate secretion of growth hormone;
- the long-term treatment of growth retardation due to Turner’s Syndrome confirmed by chromosome analysis.”

1.3. Dosage
- Growth hormone deficiency in children: 0.02 – 0.03 mg/kg/day (corresponding to 0.7 to 1.0 mg/m²/day)
- Turner syndrome: 0.050 mg/kg/day (corresponding to 1.4 to 1.63 mg/m²/day)

2 REMINDER OF THE COMMITTEE’S OPINION AND CONDITIONS OF INCLUSION

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

<table>
<thead>
<tr>
<th></th>
<th>GH deficiency in children</th>
<th>Turner syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTONORM</td>
<td>substantial</td>
<td>substantial</td>
</tr>
<tr>
<td>NORDITROPIN</td>
<td>substantial</td>
<td>substantial</td>
</tr>
<tr>
<td>NUTROPINAX</td>
<td>substantial</td>
<td>substantial</td>
</tr>
<tr>
<td>SAIZEN</td>
<td>substantial</td>
<td>substantial</td>
</tr>
<tr>
<td>UMATROPE</td>
<td>substantial</td>
<td>substantial</td>
</tr>
<tr>
<td>ZOMACTON</td>
<td>substantial</td>
<td>substantial</td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>substantial</td>
<td>substantial</td>
</tr>
</tbody>
</table>
Table 2: IAB of growth hormone proprietary medicinal product in the indications of ZOMACTON

<table>
<thead>
<tr>
<th></th>
<th>GH deficiency in children</th>
<th>Turner syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTONORM</td>
<td>II (Oct 1996)</td>
<td>IV (Dec 2011)</td>
</tr>
<tr>
<td>NORDITROPIN</td>
<td>V (May 2000)</td>
<td>IV (Dec 2011)</td>
</tr>
<tr>
<td>NUTROPINAQ</td>
<td>V (Sept 2004)</td>
<td>IV (Dec 2011)</td>
</tr>
<tr>
<td>SAIZEN</td>
<td>II (Oct 1996)</td>
<td>IV (Dec 2011)</td>
</tr>
<tr>
<td>UMATROPE</td>
<td>II (Oct 1996)</td>
<td>IV (Dec 2011)</td>
</tr>
<tr>
<td>ZOMACTON</td>
<td>II (Oct 1996)</td>
<td>IV (Dec 2011)</td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>V (Jan 2007)</td>
<td>IV (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 preparations of human recombinant growth hormone or somatropin (rh-GH)

Table 4: Indications for proprietary medicinal products containing growth hormone

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>+</td>
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<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>
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<td>no</td>
<td>no</td>
<td>+</td>
</tr>
<tr>
<td>NUTROPINAQ</td>
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<td>+</td>
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<td>no</td>
<td>no</td>
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<td>SAIZEN</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>no</td>
<td>+</td>
</tr>
<tr>
<td>UMATROPE</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>no</td>
<td>+</td>
<td>no</td>
<td>+</td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>no</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</th>
<th>95% CI Lower limit</th>
<th>95% CI Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTIONORM</td>
<td>44 (27)</td>
<td>4812</td>
<td>3390</td>
<td>6234</td>
<td></td>
</tr>
<tr>
<td>NORDITROPIN SIMPLEXX</td>
<td>41 (25)</td>
<td>4484</td>
<td>3111</td>
<td>5856</td>
<td></td>
</tr>
<tr>
<td>NUTRIPAQAQ</td>
<td>22 (14)</td>
<td>2406</td>
<td>1401</td>
<td>3411</td>
<td></td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>13 (8)</td>
<td>1422</td>
<td>649</td>
<td>2195</td>
<td></td>
</tr>
<tr>
<td>SAIZEN</td>
<td>19 (12)</td>
<td>2078</td>
<td>1144</td>
<td>3012</td>
<td></td>
</tr>
<tr>
<td>UMATROPE</td>
<td>20 (12)</td>
<td>2187</td>
<td>1229</td>
<td>3146</td>
<td></td>
</tr>
<tr>
<td>ZOMACTON</td>
<td>3 (2)</td>
<td>328</td>
<td>-43</td>
<td>699</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>161</td>
<td>17,607</td>
<td>14,888</td>
<td>20,327</td>
<td></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

1 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.

\(^2\) 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 Adulte 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

\(^8\) TA188 Human growth hormone (somatropin) for the treatment of growth failure in children: guidance - 22 July 2010 - guidance.nice.org.uk
\(^10\) Sävendahl L. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and
SAGhE 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 (SAGhE), 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 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 5 July 2006.

8 RE-EVALUATION OF ACTUAL BENEFIT

8.1. 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 ZOMACTON in children with GH deficiency remains substantial.

8.2. 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 the data studied, the actual benefit of ZOMACTON in Turner syndrome remains substantial.

8.3. Transparency Committee recommendations
The Transparency Committee recommends continued inclusion of ZOMACTON 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.

8.3.1. Packaging: Appropriate for the prescription conditions in the MA

8.3.2. Reimbursement rate: 100 %

8.3.3. 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,\(^2\) 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,\(^6\) 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 Rachmied 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 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 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/m²/day. Prior to randomisation, they had all been treated for at least one year with 0.7 mg/m²/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 Rachmied (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 ± 0.6 SDS (1001 children) at 1 year and 0.4 ± 0.4 SDS (336 children) at 2 years. For organic deficiencies, the gain in height was 0.9 ± 1.1 SDS (300 children) at 1 year and 0.4 ± 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 ± 0.9 SDS for those with idiopathic deficiencies and -2.2 ± 1.2 SDS for those with organic deficiencies.
- The mean doses of growth hormone used were 0.216 ± 0.044 mg/kg/day for those with idiopathic deficiencies and 0.212 ± 0.047 mg/kg/day for those with organic deficiencies.

Results: For idiopathic deficiencies, the gain in height was 0.7 ± 0.4 (85 children) at 1 year and 0.4 ± 0.4 (336 children) at 2 years. For organic deficiencies, the gain in height was 0.7 ± 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/SANODZ 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 5 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 ± 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-PhIIb-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 ± 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 ± 0.40 SDS, and the mean height at the end of the study was 148.8 ± 14.02 cm, i.e. 0.91 ± 0.86 SDS.
- Study EP2K-02-PhIII-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 ± 1.00 SDS. The mean height at the end of the study was 142.84 ± 14.02 cm,
i.e. -1.11 ± 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.