HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

7 December 2011

OMNITROPE 10 mg/1.5 ml, solution for injection
B/1 cartridge of 1.5 ml (CIP code: 382 944-3)
B/5 cartridges of 1.5 ml (CIP code: 382 946-6)
B/10 cartridges of 1.5 ml (CIP code: 382 947-2)

OMNITROPE 5 mg/1.5 ml, solution for injection
B/1 cartridge of 1.5 ml (CIP code: 380 548-3)
B/5 cartridges of 1.5 ml (CIP code: 380 550-8)
B/10 cartridges of 1.5 ml (CIP code: 380 551-4)

Applicant: SANDOZ SAS

somatropin
ATC Code: H01AC01

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

Date of Marketing Authorisation: 19.09.2007 and 20.04.2007 (centralised procedure)

Reason for request: Re-assessment of the actual benefit (AB) in accordance with Article R 163-21 of the social security code for children with no deficiency:

- Treatment of growth failure in girls with gonadal dysgenesis (Turner syndrome) confirmed by chromosome analysis.
- Treatment of growth failure associated with chronic renal insufficiency (CRI) in pubescent and prepubescent children.
- Treatment of growth failure (current height < - 2.5 SDS and parental adjusted height < - 1 SDS) in children who are born small for gestational age with a birth weight and/or length of < - 2 SDS, who failed to show catch-up growth (growth velocity SDS< 0 during the last year) by 4 years of age or later.
- Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.

This re-assessment does not relate to the indications involving children who are deficient in growth hormone.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Somatropin

1.2. Background

Medicinal product that is biologically similar or "biosimilar" to the proprietary medicinal product GENOTONORM®, in accordance with European recommendations.

1.3. Indications

"Children:

- Growth failure associated with growth hormone deficiency.
- Growth failure associated with growth hormone deficiency and growth failure associated with Turner syndrome or chronic renal insufficiency.
- Growth failure (current height < -2.5 standard deviation score (SDS) and parental adjusted height < - 1 SDS) in children born small for gestational age with a birth weight and/or length of < - 2 standard deviations (SD), who failed to show catch-up growth (growth velocity (GV) SDS < 0 during the last year) by 4 years of age or later.
- Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.

Adults:

Replacement therapy in adults with severe growth hormone deficiency.
Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic pituitary pathology and at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth hormone deficiency.
In patients with childhood onset growth hormone deficiency (no history of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests must be performed, except in those with low IGF-1 concentrations (SDS < -2), which can be regarded as one test.
The cut-off points of the dynamic tests should be strictly defined."

1.4. Dosage

Table 1**:** Dosage of OMNITROPE in indications in children with no deficiency

Indication	mg/kg body weight dose per day	mg/m^2 body surface area dose per day
Turner syndrome	0.045 – 0.050	1.4
Chronic renal insufficiency	0.045 – 0.050	1.4
Children born small for gestational age	0.035	1.0
Prader-Willi syndrome in children	0.035	1.0

2 REMINDER OF THE COMMITTEE'S OPINIONS IN RELATION TO NON-DEFICIENT CHILDREN

Table 2**:** AB of proprietary growth hormone products in the indications in non-deficient children

Indications Proprietary products	Turner syndrome	Renal disease in pre-pubescent children	Renal disease in pubescent children	Prader-Willi syndrome	SHOX deficiency	Growth failure in children born small for gestational age or with intrauterine growth restriction*
Genotonorm	Substantial	Substantial	Substantial	Moderate	-	Moderate
Norditropin	Substantial	Substantial	-	-	-	Moderate
Nutropinaq	Substantial	Substantial	-	-	-	-
Saizen	Substantial	Substantial	-	-	-	Moderate
Humatrope	Substantial	Substantial	-	-	Moderate	Moderate
Zomacton	Substantial	-	-	-	-	-
Omnitrope	Substantial	Substantial	Substantial	Moderate	-	Moderate

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

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

IACB (date obtained)	Turner syndrome	Renal disease in pre-pubescent children	Renal disease in pubescent children	Prader-Willi syndrome	SHOX deficiency	Growth failure in children born small for gestational age or with intrauterine growth restriction*
Genotonorm	II (Oct 1996)	II (Oct 1996)		III (Sept 2001)	-	V (Jul 2004)
Norditropin	II (Sept 1996)	II (Sept 1996)	-	-	-	V (Jul 2004)
Nutropinaq	V (Sept 2004)	V (Sept 2004)	-	-	-	-
Saizen	II (Oct 1996)	II (Nov 1998)	-	-	-	V (Mar 2006)
Humatrope	II (Oct 1996)	II (May 2000)	-	-	IV (Jul 2008)	V (Jul 2007)
Zomacton	V (Oct 2001)	-	-	-	-	-
Omnitrope	V (Jan 2007)	V (Jan 2007)		V (Jan 2007)	-	V (Jan 2007)

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2011)

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

3.2. Medicines in the same therapeutic category

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

	Growth hormone deficiency	Turner syndrome	Renal disease in pre-pubescent children	Renal disease in pubescent children	Prader-Willi syndrome	SHOX deficiency	Growth failure in children born small for gestational age or with intrauterine growth restriction*
Genotonorm	+	+	+	+	+	No	+
Nutropinaq	+	+	+	No	No	No	No
Saizen	+	+	+	No	No	No	+
Humatrope	+	+	+	No	No	+	+
Zomacton	+	+	No	No	No	No	No
Omnitrope	+	+	+	+	+	No	+

4 DRUG USE DATA

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

Usage data are available for the indications: children born small for gestational age, Turner syndrome and chronic renal insufficiency.
In Prader-Willi syndrome, no source of data on the use of growth hormone has been identified. No study has been requested by HAS or the health authorities in Prader-Willi syndrome.

<u>Children born small for gestational age</u>

At the request of the Transparency Committee, seven post-registration studies were commenced between 2004 and 2007. The definitive results are available for two of them, and the other five are still underway.
The low follow-up rate for the patients included in the two studies does not permit a conclusion about the effect of growth hormone on growth and the final height of the children, or about tolerability. The criteria for commencing treatment appear to have been followed in one study (Maxomat), in contrast to the other (Zomacton). The administration procedures (dosage, frequency of injections) were in accordance with the recommendations.

In relation to the data on use, a study by CNAMTS, published in 2004, is also available:
1500 patients treated (estimate for the whole of France, twice as high as the figure expected by the Transparency Committee), mean age 9.9 years, severe associated disorders (mainly malformation or chromosomal abnormality, neurological disease or metal retardation and endocrine or metabolic diseases) in 18% of cases, criteria for starting treatment did not conform with the SPC in 44% of cases (height or age), mean increase in height (after 3 years of continuous treatment) + 1.5 SD, criteria for discontinuation of treatment (according to the SPC) not respected in 8% of patients (increase in height in the last year of treatment, bone and height age), dosages between 1.1 and 1.3 IU/kg/week in 77% of cases (more than 1.3 IU/kg/week in 9% of patients treated), most frequent reasons for discontinuation: achievement of desired height, bone age limit passed, decision of the patient or his/her family, inadequate response to treatment.
The authors stated that the treatment was frequently carried out outside the criteria defined by the SPC, probably because of the different thresholds set in the Marketing Authorisation and the SPC. They stressed, in particular, the existence of a *continuum* between children born small for pathological reasons known or assumed *a posteriori* and children born small in a family of constitutionally small stature who do not present any specific pathological condition. Finally, in this indication, the heterogeneous character of the population (isolated IUGR suggests isolated familial short stature, children born small for gestational age who present associated disorders) limit the measurement and interpretation of treatment results.

Turner syndrome and chronic renal disease

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

- *Turner syndrome:* Almost 900 patients treated (estimate for the whole of France), mean age 12.5 years, severe associated disorders (mainly cardiac or pulmonary malformation) in 9% of cases, criteria for starting treatment (bone age < 12 years according to the SPC) not respected in 6% of cases, mean duration of treatment 5.6 years, mean total increase in height + 2.35 SD with respect to the Turner growth charts and + 1.06 SD with respect to the reference growth charts, criteria for discontinuation of treatment (according to the SPC) not respected in 13% of patients (increase in height in the last year of treatment, bone and height age), dosages between 0.7 and 0.9 IU/kg/week in 77% of cases (more than 0.9 IU/kg/week in 15% of patients treated) most frequent reasons for discontinuation: bone age limit passed, inadequate treatment response, decision of the patient of his/her family.
- *Chronic renal disease* (only for the indication “prepubescent children”): About 220 patients treated (estimate for the whole of France), mean age 11.1 years, severe associated disorders (disorder caused by or associated with CRD) in 28% of cases, criteria for starting treatment (height, age, bone age, signs of puberty) defined by the SPC not respected in 60% of cases[1], mean duration of treatment 4 years, mean total increase in height + 1.1 SD over the mean duration of treatment, criteria for discontinuation of treatment in the SPC not respected in 18.5% of patients (increase in height in the last year of treatment, bone and height age), mean dosage 1.04 IU/kg/week, most frequent reasons for discontinuation: mainly logical consequence of kidney transplantation.

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

[1] The authors note that it is possible that, in the context of chronic renal disease, the appearance of a break in the growth curve could lead the clinician to start treatment early because the course appears inevitable. This view was confirmed by work group conducting this assessment.

5 DATA ON TREATMENT PROCEDURES WITH GROWTH HORMONE IN EUROPE

Table 5, below, details the European countries in which each of the propriety medicinal products on the market in France is refundable (in which indications, and at what level) together with special conditions of the availability of reimbursement. According to this information, it appears that:

- All European counties provide growth hormone treatment for Turner syndrome and renal disease.
- The indications SHOX, SGA and Prader-Willi syndrome are not treated in all countries.
- If they are treated, the whole cost of treatment is covered.

Table 5: Treatment with growth hormone and terms of reimbursement in Europe

	Turner syndrome	Renal disease	Prader-Willi syndrome	SHOX deficiency	SGA	Comments
Germany	100%	100%	100%	100%	100%	
Austria	100%	100%	100%	0	0	
Belgium	100%	100%	100%	0	100% if H < - 2 SDS	Prescribers limited to university specialists
Denmark	100%	100%	100%			
Spain	100% if H < -2 SDS age ≥ 2 years	100% if H < -2 SDS age ≥ 2 years	100%	100%	100% if H < - 2.5 SDS and GR = 0	
Estonia	100%	100%	100%	0	100%	Limited to children whose growth has not stopped
Finland	42%	100%	42 %	0	42%	
Greece	100% if age ≥ 2 years	100% if age ≥ 2 years	100%			
Ireland	100%	100%	100%	0	100%	No check of compliance with indications
Italy	100%	100%	100% if: 1/deficient, 2/ age prepubescent, 3/ IMC<25, 4/ respiratory function normal	0	100%	Refundable for 2 years, extended on the advice of a regional committee
Luxembourg	100%	100%				
Latvia	100%	100%	100%	0	100%	
Malta	100%	100%	0	0	100%	
Norway	Refundable from case to case	Refundable from case to case	If deficient			36%, with a ceiling of 56 Euros/T)
Netherlands	100% if: H < -1.5 SDS age ≥ 6 years	100% if: 1/H < -1.3 SDS of parental height 2/Reduction in GR ≥ 0.25 SDS/year	100%			
Poland	100%	100%	100%			
Portugal	100%	100%	100%	0	100%	Assessment of each patient's file by a committee
Czech R.	100%	100%	100%	100%	100%	
Romania	50% H < -2.5 SDS	100%				
United Kingdom	100%	100%	100%	100%	100%	
Sweden	100%	100%	100%	100%	100%	
Slovakia	100%	100%	100%	100%	100%	
Slovenia	100%	100%	100%	100%	100%	Indications refundable not defined, a single prescription point in the country

6 UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

In 2007, during the reassessment of some proprietary growth hormone products in the indication "growth failure in children born small for gestational age who failed to show catch-up growth by the age of 4 years or later", the Transparency Committee considered the demonstration of the benefit of this treatment in terms of the improvement in final height and the uncertainties relating to long-term tolerance of such treatment. The commission also considered the fact that small stature may not, of itself constitutes, a medical condition.

The reassessment was based on the data contained in the HAS report "L'hormone de croissance chez l'enfant non déficitaire" [Growth hormone in non-deficient children] (available under http://www.has-sante.fr) and the opinion of an expert from outside the working group.
The HAS report was compiled on the basis of:

- all the literature data published up to May 2010,
- a meta-analysis of the clinical studies into the efficacy in respect of height, sponsored by HAS,
- the data supplied by the pharmaceutical companies,
- the opinion of a multidisciplinary working group,
- the recent results of a French tolerance study (SAGHE)[2]
- the observations, recorded as appropriate, made in the course of the hearing by patients' associations and healthcare professionals concerned with these rare conditions.

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

6.1. Efficacy of growth hormone in non-deficient children

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

6.1.1. Turner syndrome

- Meta-analysis of clinical studies

In Turner syndrome, the meta-analysis commissioned by HAS identified 11 randomised studies, with 12 comparisons and a total of 781 patients. The comparisons carried out were:

- growth hormone (GH) versus untreated,
- GH versus placebo,
- a "fixed dose" versus an "increasing dose" scheme,
- "3 injections per week" versus "6 injections per week",
- "1 injection per day" versus "2 injections per day",
- "increasing dose" versus "fixed dose".

The mean population was 65 patients per group (between 9 and 78 per group). The first study was published in 1989, the last in 2007. Only one study was double blind, and 11 were

[2] In November 2010, the results of the study "Santé Adulte GH Enfant" (SAGHE; Adult health following childhood GH) to evaluate the long-term mortality and morbidity of children exposed to growth hormone were presented. This relates to unpublished data made public by Afssaps in the form of an oral communication following a press conference organised by Afssaps in December 2010, an assessment of the risk/benefit ratio conducted by the EMA, the initials results of which were made public in May 2011, and the reassessment carried out by the FDA that was made public in April 2011.

open. All the studies included were reported in English. In addition to the studies included, 33 studies were excluded. No unpublished studies were identified. No studies that were in progress at the time were identified by checking the registers and other sources.

The study data that were included related to the following criteria:

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

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

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

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

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

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

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

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

- change of height (cm): WMD = -2,70, 95% CI between -4.66 and -0.74, $p = 0.0069$, 1 study and,
- change of height SDS: WMD = -0.30, 95% CI between -0.52 and -0.08, $p = 0.0082$, 1 study.

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

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

[3] WMD : weighted mean difference.

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

- final height SDS: WMD = 0.95, 95% CI between 0.51 and 1.39, p < 0.0001, 2 studies,
- final height (cm): WMD = 5.50, 95% CI between 2.73 and 8.28, p < 0.0001, 2 studies,
- change of height SDS: WMD = 0.53, 95% CI between 0.30 and 0.75, p < 0.0001, 2 studies, and
- change of growth rate SDS: WMD = 0.93, 95% CI between 0.50 and 1.37, p < 0.0001, 2 studies.

- Observational studies

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

6.1.2. Chronic renal disease

- Meta-analysis of clinical studies

In renal disease, the meta-analysis commissioned by HAS identified 13 randomised studies, with 16 comparisons and a total of 665 patients. The comparisons carried out were:

- growth hormone (GH) versus placebo,
- GH versus untreated,
- high dose (56 IU/m^2/week) versus low dose (28 IU/m^2/week),
- high dose (28 IU/m^2/week) versus low dose (14 IU/m^2/week).

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

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

The data related to the following criteria:

- growth rate (1 year) (11 studies),
- change of height SDS (9 studies),
- change of growth rate SDS (7 studies),
- change of growth rate (cm/year) (4 studies),
- height at the end of the study SDS (4 studies),
- growth rate SDS (3 studies),
- change of height (cm) (1 study).

In the GH versus placebo comparison, GH was better than placebo in terms of:

- height at end of study SDS: WMD[4] = 1.36, 95% CI between 0.86 and 1.86, p < 0.0001, 1 study,
- change of height SDS: WMD = 1.18, 95% CI between 0.74 and 1.62, p < 0.0001, 1 study,
- growth rate (1 year): WMD = 4.20, 95% CI between 2.92 and 5.48, p < 0.0001, 1 study,
- change of growth rate SDS: WMD = 7.80, 95% CI between 6.09 and 9.51, p < 0.0001, 2 studies.

[4] : WMD: weighted mean difference.

In the GH versus untreated comparison, GH was better than untreated in respect of:
- height at end of study SDS: WMD = 0.73, 95% CI between 0.33 and 1.12, p < 0.0001, 3 studies,
- change of height (cm): WMD = 3.80, 95% CI between 2.51 and 5.09, p < 0.0001, 1 study,
- change of height SDS: WMD = 0.72, 95% CI between 0.51 and 0.93, p < 0.0001, 4 studies,
- growth rate (1 year): WMD = 3.76, 95% CI between 3.12 and 4.39, p < 0.0001, 6 studies,
- change of growth rate SDS: WMD = 6.14, 95% CI between 3.42 and 8.86, p < 0.0001, 2 studies.

In the high dose (56 IU/m^2/week) versus low dose (28 IU/m^2/week) comparison, no statistically significant difference was observed in terms of:
- change of height SDS: WMD = 0.30, 95% CI between -1.00 and 1.60, p = 0.6522, 1 study,
- growth rate (1 year): WMD = 1.10, 95% CI between -1.23 and 3.43, p = 0.3543, 1 study,
- change of growth rate (cm/year): WMD = 1.10, 95% CI between -1.23 and 3.43, p = 0.3543, 1 study.

In the high dose (28 IU/m^2/week) versus low dose (14 IU/m^2/week) comparison, no statistically significant difference was observed for change of height SDS (WMD = 0.17, 95% CI between -0.14 and 0.49, p = 0.2784, 3 studies). Nevertheless, the high dose (28 IU/m^2/week) is better than the low dose (14 IU/m^2/week) in terms of:
- growth rate (1 year): WMD = 1.34, 95% CI between 0.55 and 2.13, p < 0.0001, 3 studies,
- growth rate SDS: WMD = 1.30, 95% CI between 0.30 and 2.30, p = 0.0108, 3 studies,
- change of growth rate (cm/year): WMD = 1.34, 95% CI between 0.55 and 2.13, p < 0.0001, 3 studies,
- change of growth rate SDS: WMD = 1.30, 95% CI between 0.30 and 2.30, p = 0.0108, 3 studies.

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

- Observational studies

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

6.1.3. SGA children

- Meta-analysis of clinical studies

In SGA, the meta-analysis commissioned by HAS identified 10 randomised studies, with 13 comparisons and a total of 996 patients. The comparisons carried out were:
- a dose of 0.033 mg/kg/d versus 0.067 mg/kg/d,
- intermittent treatment alternating treatment years and observation years for 4 years versus 2 years of treatment followed by 2 years of observation,
- a tailored dose versus a fixed dose,
- growth hormone versus untreated,
- growth hormone at a dose of 3 IU versus 6 IU.

None of the studies identified was excluded from the meta-analysis. No studies that were in progress at the time were identified by checking the registers and other sources.

The mean population was 76 patients per group (between 12 and 102 per group). The first study was published in 1997, the last in 2009. Only one study was double blind, and 8 were open. All the studies included were reported in English. No unpublished studies were identified.

The data related to the following criteria:

- growth rate SDS (16 studies),
- height at the end of the study SDS (6 studies),
- change of height (cm) (3 studies),
- final height SDS (1 studies),
- height at the end of the study (cm) (2 studies),
- growth rate (1 year) (1 study).

In the GH at a dose of 0.033 mg/kg/d versus 0.067 mg/kg/d comparison, no significant difference was observed for:

- height at end of study (cm): WMD = -2.40, 95% CI [-6.78; 1.98], p = 0.2833, 1 study,
- height at end of study SDS: WMD = -0.30, 95% CI [-0.76; 0.16], p = 0.1972, 1 study.

In the same comparison, GH 0.033 mg/kg/d is worse than GH 0.067 mg/kg/d in terms of:

- change of height (cm): WMD = -1.60, 95% CI [-2.25; -0.95], p < 0.0001, 1 study,
- growth rate SDS: WMD = -2.10, 95% CI [-3.04; -1.16], p < 0.0001, 1 study.

In the comparison between two different intermittent treatment schemes over a period of 4 years: alternation between one year of treatment and one year of observation (GH TO/TO) and 2 years of treatment followed by 2 years of observation (GH TT/OO), no statistically significant difference was observed between GH TO/TO and GH TT/OO in terms of:

- height at end of study SDS: WMD = 0.00, 95% CI [-0.46; 0.46], p = 1.0000, 1 study,
- growth rate SDS: WMD = -0.60, 95% CI [-1.24; 0.04], p < 0.0657, 1 study.

The available data are insufficient to compare the tailored dose GH versus fixed dose GH. The eligible study did not report sufficient information about the assessment criteria considered by this meta-analysis.

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

- final height SDS: WMD = 0.60, 95% CI [0.23; 0.97], p < 0.0001, 1 study,
- height at end of study SDS: WMD = 1.19, 95% CI [0.97; 1.41], p < 0.0001, 3 studies,
- change of height (cm): WMD = 8.52, 95% CI [7.75; 9.30], p < 0.0001, 2 studies,
- growth rate (1 year): WMD = 5.30, 95% CI [4.32; 6.28], p < 0.0001, 1 study,
- growth rate SDS: WMD = 5.45, 95% CI [4.93; 5.98], p < 0.0001, 4 studies.

In the GH 3 IU versus GH 6 IU comparison, no significant difference was observed for the final height SDS (WMD = -0.20, 95% CI [-0.63; 0.23], p = 0.3587, 1 study). However, GH 3 IU is worse than GH 6 IU in terms of the height at end of study SDS (WMD = -0.40, 95% CI [-0.71; -0.09], p = 0.0112, 1 study).

In summary, in children born small for gestational age, the meta-analysis of the clinical studies to evaluate the efficacy of growth hormone suggest that these treatments are beneficial with respect to placebo or no treatment in terms of:

- growth rate,
- height (at end of study or change between the start and end of the study).
    - For adult height, according to one study, the treatment effect SDS is +0.6 [0.23-0.97]) in this indication (dose: 0.067 mg/kg/d). It should be noted that this study in children with an average age of 12.7 years does not reflect actual practice, which is to carry out treatment at an earlier age.
    - For height at the end of the study, on the basis of three studies that lasted 2 years (with doses of 66 µg/kg/d or 0.2 or 0.1 IU/kg/d) the meta-analysis showed a treatment effect SDS of 1.19. The effect of GH on height after 2 years was greater that the effect on adult height.

In this indication, the meta-analysis suggests that, in terms of the dose-effect relationship, a more intense treatment results in a greater effect on height at the end of treatment. There is no evidence in favour of a dose-related effect on adult height.

- Observational studies

Three observational studies, including one unpublished study (KIGS cohort), contain data on adult height or for the duration of long-term prescription. In the two studies with data on adult height, the results are as follows: increase SDS of 1.3 with respect to initial height in the first study [Dahlgren 2005] and 1.82 with respect to an untreated group in the second study [Van Dijk 2007]. Even though the results of these studies do not prove the efficacy of growth hormone in respect of adult height, they are nevertheless compatible with the increase in adult height observed in the meta-analysis.

6.1.4. Prader-Willi syndrome

- Meta-analysis of clinical studies

In Prader-Willi syndrome, the meta-analysis requested by HAS identified 6 randomised studies that made 6 comparisons and included 244 patients. All the studies concerned the assessment of growth hormone (GH) versus no treatment. The mean group size was 28 patients per group (between 6 and 35 per group). The first study was published in 1997, the last in 2009. All studies were open. All the studies included were reported in English. No unpublished studies were found. No ongoing studies were identified by the search in the registries or other sources.

One study was excluded from the analysis because of its non-randomised nature. It was the study by the Swedish National Growth Hormone Advisory Group of 1997.

The data from the studies included concerned the following criteria:
- growth velocity in SDS (2 studies),
- change in height in cm (2 studies),
- height at end of study in SDS (1 study).

In the comparison GH versus no treatment, GH is superior to no treatment in terms of:
- height at end of study in SDS: WMD=1.00, 95% CI between 0.33 and 1.67, p=0.0035, 1 study,
- change in height (cm): WMD=5.37, 95% CI between 4.36 and 6.38, p<0.0001, 2 studies,
- growth velocity in SDS: WMD=4.48, 95% CI between 3.61 and 5.34, p<0.0001, 2 studies.

- Observational studies

The data from the KIGS cohort made it possible to observe an effect of GH on adult height of 1.24 SDS (in 61 children). Although the results of these studies do not demonstrate the efficacy of growth hormone on adult height, they are still consistent with the gain in adult height found in the meta-analysis. This study also concludes that there is an effect of growth hormone on weight in patients with Prader-Willi syndrome.

6.2. Clinical relevance of the size of effect observed in the studies

In adults, one standard deviation (SD) in height represents 5.6 cm (women) or 6 cm (men).

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

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

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

In the absence of treatment, the epidemiological data indicate that the mean adult height for the various indications concerned is 1 m 43 (Turner syndrome), 1 m 65 for men and 1 m 54 for women (children born small for gestational age who failed to show catch-up growth by the

age of 4 years), 1 m 54 for men and 1 m 45 – 1 m 49 for women (Prader-Willi syndrome), 1 m 56 for men and 1 m 52 for women (chronic renal disease).

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

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

6.3. Long-term tolerance

- Epiphysiolysis

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

- Risk of diabetes

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

- Risk of cancer

In respect of the risk of cancer, even though the publically available data do not permit formal confirmation of an increased risk of death from and/or the occurrence of cancer due to growth hormone in non-deficient children compared with the general population, they do not disprove it either[5].

- Risk of mortality

In November 2010, the results of the French SAGHE study[2] to evaluate mortality and long-term morbidity in children exposed to growth hormone were presented. These are unpublished data made public by Afssaps in December 2010. The presentation of this study led to the reassessment of the benefit-risk ratio of growth hormone by the EMA in May 2011 and by the FDA in April 2011, which was confirmed as favourable.

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

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

This risk is particularly high in patients who received high doses, above those recommended in the current Marketing Authorisation. The data do not show any increase in global mortality

[5] One study carried out in patients, most of whom were deficient, treated which growth hormone obtained by extraction, concluded that there was the risk of colorectal cancer and Hodgkin's lymphoma is 15 times higher in patients with no history of cancer or identified cancer risk factors compared with the general population of the same age.

due to cancer (all cancers together). They do, however, suggest increased mortality due to the occurrence of cerebrovascular complications (such as intracerebral haemorrhages) and bone cancers.

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

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

Even though these results constitute a signal, the design and nature of the study means that they do not establish a causal relationship between mortality and the GH treatment. Other factors may be associated with the increased mortality observed in the population studied.
Taking into consideration the French SAGHE study, the EMA and the FDA concluded that the benefit-risk relationship is still favourable, that strict observation of the indications is necessary, that the doses in the Marketing authorisation must not be exceeded, and that it is necessary to wait, before reaching a definitive conclusion, for the results of the European SAGHE study.

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

SGA
No specific effects of GH have been described in this indication.

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

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

Prader-Willi syndrome
The profile of adverse effect of growth hormone, insulin resistance, diabetes, etc., is essentially due to the weight gain. These effects are present in the natural history of the syndrome, and may, in some cases, particularly at the start of treatment, be aggravated by growth hormone.
Cases of sudden death have also been reported in patients with Prader-Willi syndrome. The studies do not show clearly whether their frequency is higher in patients treated with GH, but, in treated patients, an analysis of the cases revealed a higher frequency (75% of cases) of sudden death in the first 9 months of growth hormone treatment than during the rest of the treatment. This increase in the risk of sudden death at the start of treatment appears to be related to obesity and or tonsillar or adenoid hypertrophy.

6.4. Is small stature a pathological condition?

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

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

According to the second definition, a pathological condition is defined as a physical or mental process that tends to affect the wellbeing of the individual such as his or her ability to act and achieve his or her objectives within his or her environment. From this point of view, short

stature could be considered a pathological condition if it affects an individual to the point of disturbing his or her global development in a physical, psychological and social sense.

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

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

6.5. Conclusion

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

- in Turner syndrome, an increase in height versus untreated of +1.15 SDS [0.73; 1.57], or of the order of +6.5 cm.
- in chronic renal disease, the final height is not available; instead, the target variable is the increase in height under GH before transplantation. The increase in height under GH versus untreated at the end of the study is +0.73 [0.33;1.12].
- in SGA children, an increase in height versus untreated of +0.6 SDS [0.23; 0.97], or of the order of 3 to 4 cm.

The results of the available observational studies are similar.

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

The Committee wants the use of growth hormones to follow good practice, that is to say:

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

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7 TRANSPARENCY COMMITTEE CONCLUSIONS

7.1. Reassessment of actual benefit

Growth failure due to Turner syndrome:

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

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

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

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

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

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

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

Taking into account all the data studied, the actual benefit of OMNITROPE in Turner syndrome is **substantial**.

Growth failure due to chronic renal disease:

Chronic renal disease in children is a rare but serious illness with a variable course, depending on the aetiology, and can sometimes lead to the death of the child. Short stature is just one feature of this illness, and may contribute to a marked deterioration of the quality of life.

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

The efficacy of growth hormone on height at the end of the study in chronic renal disease has been demonstrated, and confirmed in other studies with different height parameters. Observational studies confirm the efficacy that was observed in the clinical studies. During the short period of the study before the transplant, the increase in height is small, but forms part of the necessary global treatment.
There is a tolerance signal suggesting increased mortality in adults who have used growth hormone during childhood. Supplementary studies are required to reach a conclusion.

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

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

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

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

Growth failure in children born small for gestational age:

Growth failure in children born small for gestational age (SGA) who failed to show catch-up growth by the age of 4 years is characterised by isolated short stature the origin of which has not been identified.

This proprietary medicinal product falls within the framework of a 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 with different height parameters. The increase in height is small. Observational studies confirm the low efficacy that was observed in the clinical studies.
There is a tolerance signal suggesting increased mortality in adults who have used growth hormone during childhood. Supplementary studies are required to reach a conclusion.

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

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

Public health benefit:
The growth failure in children born small for gestational age who failed to show catch-up growth by the age of 4 years or more is a minor burden in terms of public health in view of the limited number of patients involved.
This illness falls within the category of rare illnesses, its treatment is a public health need (Second National Rare Diseases Plan, 2010-2014).
According to the available data, the effect of growth hormone treatment on the final height of the children is at most small. The effect of the treatment on adult height has not been established. The impact at the psychological, social and quality of life level has not been established.
Moreover, a negative effect cannot be ruled out, particularly because searches indicate the long-term risk of cancer, diabetes and cardiovascular diseases.
In addition, there is no guarantee that the data from clinical studies can be transposed to clinical practice, particularly in view of the observance problems linked to the long-term need for daily injections.
As a result, growth hormone treatment will not provide any public health benefit in the treatment of growth failure in children born small for gestational age with a birth weight and/or length < - 2 SD, who failed to show catch-up growth (growth rate < 0 SD during the last year) by the age of 4 years or more.

The actual benefit of OMNITROPE in children born small for gestational age with a birth weight and/or length of < -2 SD who failed to show catch-up growth (growth rate < 0 SD during the last year) by 4 years of age or later and with growth failure (current height less than or equal to -3 SD and parental adjusted height < -1 DS) is **low**.

Prader-Willi syndrome:
Prader-Willi syndrome is a rare disease of genetic origin combining statural and pubertal growth failure, learning difficulties and behavioural disorders and in particular eating disorders with obesity. Only a small proportion of these patients (of the order of 20 to 30%) have no growth hormone deficiency. Individuals' weight and morphological characteristics have the greatest effect on quality of life for those with Prader-Willi syndrome. The life expectancy of persons with Prader-Willi syndrome is limited because of the numerous complications of the disease.

This proprietary medicinal product is intended as curative treatment for short stature, as part of the overall management of the disease.

The efficacy of growth hormone on height and physical constitution in Prader-Willi syndrome has been demonstrated in short-term clinical studies. Some studies show that GH promotes the child's psychomotor development.
There is a tolerance signal which gives reason to suspect excess mortality in adults who used growth hormone in their childhood. Additional studies are needed before any conclusion can be reached.

The efficacy/tolerance ratio of this proprietary medicinal product in this indication is **modest**.

There is no pharmacological alternative to somatropin for an effect on height.

Public health benefit:
Prader-Willi syndrome is a low public health burden because of the limited number of patients concerned.
Since this disorder is a rare disease, its management is a public health need (Second National Rare Disease Plan 2010-2014).
This disease needs global, multidisciplinary management in which growth hormone treatment is just one aspect.
In view of the available data, the impact of growth hormone treatment on children's height is at best low. The impact of treatment on adult height and on body mass index has not been established. Psychologically, socially and as regards quality of life, this impact has not been established.
In addition, a negative impact cannot be ruled out particularly because of concerns about the long-term risk of cancer, diabetes and cardiovascular disease.
Moreover, the transferability of study data is not assured, particularly given the compliance problems linked to the need for daily injections over a long period.
Consequently, growth hormones are of no public health interest in the treatment of Prader-Willi syndrome.

The actual benefit of OMNITROPE in Prader-Willi syndrome is **substantial**.

7.2. Improvement in actual benefit (IAB)

OMNITROPE provides a minor improvement in actual benefit (IAB IV) in the management of Turner syndrome, chronic renal insufficiency and Prader-Willi syndrome.

OMNITROPE does not bring about an improvement in actual benefit (IAB V) in the therapeutic strategy in children born small for gestational age.

7.3. Target population

Estimates of the size of the maximum theoretical prevalent target populations

Born SGA with no catch-up growth (height in SDS < - 3) at 4 years of age	2200
Turner syndrome	1660
Prader-Willi syndrome	790
Chronic renal insufficiency	100

7.4. Transparency Committee recommendations

The transparency Committee recommends continued inclusion of OMNITROPE 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 all its indications in children with no deficiency.

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

The Committee points out that it wishes to receive the results of the ongoing post-inclusion study in the indication "treatment of growth failure in children born small for gestational age".

The Committee will pay particular attention to the quality of the results presented (missing data, patients lost to follow-up).

7.4.1. Packaging: Appropriate for the prescription conditions of the MA

7.4.2. Reimbursement rate: 65 %