Consensus

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Recommendations for treatment with recombinant human growth hormone in pediatric patients in Colombia

Recomendaciones para el uso de la hormona de crecimiento humana recombinante en pacientes pediátricos de talla baja en Colombia

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Abstract

In Colombia there are no guidelines for diagnosis and management of patients with short stature and for the use of recombinant human growth hormone, mainly caused by the diversity of training centers in pediatric endocrinology. In response to this situation, the Colombian College Association of Pediatric Endocrinology (*Asociación Colegio Colombiano de Endocrinología Pediátrica*) leds the first Colombian short stature expert committee in order to standardize the use of human recombinant growth hormone. This work had the participation and endorsement of a consortium of clinical experts representing the Colombian Society of Pediatrics (*Sociedad Colombiana de Pediatría*), Bogota Health District Secretariat- Southwestern Health Services Integrated Subnetwork (*Secretaría Distrital de Salud de Bogotá- Subred Integrada de Servicios de Salud Suroccidente*), Sanitas University Foundation (*Fundación Universitaria Sanitas*), University of los Andes (*Universidad de los Andes*) and some public and private health institutions in the country, in addition to the participation of methodological experts from the Keralty Global Institute of Clinical Excellence (*Instituto Global de Excelencia Clínica Keralty).* By reviewing the literature and with the best available evidence, we proposed to unify definitions, a diagnostic algorithm, biochemical and dynamic tests with their reference parameters, a description of the considerations about growth hormone use among the indications approved by regulatory agency for medications and food in Colombia and finally a proposal for an informed consent and a medication fact sheet available for parents and patients.

Keywords: Body height, growth disorders, human growth hormone, endocrine diagnostic techniques, endocrine system diseases, pediatrics.

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Resumen

En Colombia, actualmente no existen parámetros claros para el diagnóstico de pacientes con talla baja, ni sobre el tratamiento de esta población con hormona de crecimiento recombinante humana (somatropina), lo cual se ve favorecido por la diversidad de programas de formación de profesionales en endocrinología pediátrica. En respuesta a esta problemática se realizó el primer acuerdo colombiano de expertos en talla baja liderado por la Asociación Colegio Colombiana de Endocrinología Pediátrica (ACCEP); este trabajo contó con la participación y el aval de expertos clínicos de importantes instituciones de salud públicas y privadas del país, además de expertos metodológicos del instituto Keralty, quienes garantizaron la estandarización del uso de la somatropina. Después de realizar una minuciosa revisión de la literatura, se propone la unificación de definiciones, un algoritmo diagnóstico, los parámetros de referencia de las pruebas bioquímicas y dinámicas, una descripción de las consideraciones de uso de la somatropina para el tratamiento de las patologías con aprobación por la entidad regulatoria de medicamentos y alimentos en Colombia y, por último, un formato de consentimiento informado y de ficha técnica del medicamento.

Palabras clave: estatura, trastornos del crecimiento, hormona de crecimiento humana, técnicas de diagnóstico endocrinológico, enfermedades delsistema endocrino, pediatría.

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Introduction

Short stature (SS) in pediatric age may be a sign of an underlying disorder which requires proper diagnosis and treatment [1,2]; its prevalence ranges between 2.23% and 5.12%, with important differences between the level of socioeconomic development, countries and urban and rural regions.[3,4]

In Colombia, the National Survey of the Nutritional Situation 2015[5] indicates a prevalence of delay in height or in growth of 10.8% in children under 5 years of age, of 7.4% in children between 5 and 12 years and of 9.7% in children between 13 and 17 years.[6] Although the nutritional causes of SS in children do not suppose hormonal treatment, given the socioeconomic conditions or the ethnic origin and the inequity that exists in different regions of the country, it is important to take into account these causes in the diagnostic approach.

Most cases of children with SS correspond to variants of normality, being estimated that only about 20% of cases correspond to children with pathological SS[7-9] Therefore, the challenge is to identify the latter group of patients to facilitate decision-making about the need for specific diagnostic tests and indications for treatment with recombinant human growth hormone (somatropin).

Among the causes of pathological SS are endocrine disorders, which correspond to 5-10% of all cases. The most frequent of these disorders is the growth hormone deficiency (GHD), which affects mainly men with a 4:1 ratio and has a prevalence which may range from 1 case per 3,480 children, up to 1 case per 30,000 children.[9-11] In Colombia, specific data on the frequency of GHD are not known.[12]

Somatropin therapy is the approved treatment for a number of growth-related conditions, the most

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common being GHD. Other indications for this treatment differ depending on the countries and the available formulations of the hormone.[2,13] In Colombia, its use is approved for GHD, Turner syndrome (TS), small for gestational age (SGA) newborn without growth recovery or without catch-up growth, Prader-Willi syndrome (PWS) and chronic kidney disease (CKD) in children under 18 years of age, the last condition being the only one included in the health benefits plan (Annex 1).[14,15]

Just like the European Medicine Agency,[16] the Colombian National Food and Drug Surveillance Institute (INVIMA, *Instituto Nacional de Vigilancia de Medicamentos y Alimentos*), as a regulatory entity in Colombia, has not yet authorized the use of somatropin for patients diagnosed with Idiopatic Short Stature (ISS). There is also no approval for conditions that are authorized in other countries such as deficiency of the Short Stature HOmeboX-containing gene (SHOX),[2,13] or for the management of familial SS or for the increase in muscle mass in high-performance athletes or for aesthetic conditions; in the latter cases there is no certainty that the benefits outweigh the long-term risks.[17-19]

According to the records of the Drug Price Information from Colombia,[20] in 2014 the average cost of the microgram of somatropin was COP$24.83 and according to the analysis of the Institute of Health Technology Assessment, the average annual cost of the treatment per patient for that same year was COP$11,269,325, which is equivalent to USD$2,800 as of April 2020.[21] The above implies a high impact on the use of healthcare system resources and a great responsibility of the medical and scientific community for the adequate prescription of this treatment.

It should be mentioned that the international currents of pediatric endocrinology, which have a healthy heterogeneity, influence medical practice in the Colombian territory, which is why efforts have been made to put these guidelines into practice in the context of the country, such as the initiative of the University of Antioquia to formalize in 2007 the first national postgraduate degree in this specialty. Nevertheless, there are barriers to patients' access to consultation with pediatric endocrinologists and/or to perform specialized laboratory tests and dynamic tests in some regions of the country.

As for the interpretation of the results of the biochemical tests, it is necessary to point out that there is uncertainty around the reference values (especially in those requested to determine GHD), false expectations of patients and relatives and even medical-legal repercussions, which makes the approach to a patient with SS and the requirement of hormonal treatment a complex problem. These and other considerations were taken into account in an analysis of the situation with representatives of scientific societies, Colombian College Association of Pediatric Endocrinology (ACCEP, *Asociación Colegio Colombiano de Endocrinología Pediátrica*), Colombian Society of Pediatrics (SCP, *Sociedad Colombiana de Pediatría*)—, state entities —Bogota Health District Secretariat (*Secretaría Distrital de Salud de Bogotá*), universities —Sanitas University Foundation (*Fundación Universitaria Sanitas*) and Los Andes University (*Universidad de los Andes*)— and clinical experts from some public and private healthcare institutions in the country —*Hospital Infantil Concejo de Medellín*, *University IPS*, *Hospital Pablo Tobón Uribe*, *Hospital Militar Central* and Santa Fe de Bogota Foundation (*Fundación Santa Fe de Bogotá*)— for the identification and prioritization of the scenarios of greater uncertainty that were addressed in this publication.

This work aimed to present the fundamental principles of good clinical practice for the use of somatropin in pediatric patients. In this sense, the most appropriate recommendations established based on the best available evidence are presented in order to facilitate their implementation in the clinical, social and regulatory context of medical practice in Colombia.

Methodology

A study which integrated the best available evidence was carried out in order to inform each of the problems related to the use of somatropin in

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pediatric patients. In a first phase, the leader of the study conducted a SWOT (strenghts, weaknesses, opportunities and threats) analysis to identify and prioritize the scenarios of greatest uncertainty. In the next phase, which lasted about three months, each scenario was addressed in multiple work sessions (virtual and face-to-face) by a base team made up of five people (three pediatric endocrinologists and two epidemiologists). When the nature of the problem allowed, questions were formulated under the PICO structure (population, intervention, comparison, and outcome) to guide the search for relevant literature. In the other cases, and when it was not possible to identify primary or secondary studies, guiding questions were formulated to retrieve full-text documents from government agencies, ministries of health, scientific societies, health technology assessment agencies and sites for collection and development of clinical practice guidelines (CPG).

In a preliminary way, 27 questions of clinical interest were defined and then they were discussed in a face-to-face session with 25 members of the ACEP and three of the SCP, who approved the inclusion of 22 questions through anonymous electronic voting of a single round. Agreement or disagreement was considered if the results were > 70% and partial agreement if they were <70%. Of the total number of questions, four were discarded and it was suggested the revision and rethinking of three. At the end, the inclusion of a new question in the same session and an additional question included during the virtual review phase, were formulated and approved, for a total of 22 clinical questions.

From the search for evidence and the definition of the questions, full text documents were reviewed, extracting and interpreting the most relevant results and conclusions, and analyzing them with the base team of experts taking into account their degree of applicability in the Colombian context. No statistical method was applied for data analysis in this investigation. Subsequently, the recommendations were formulated, supported by the consulted evidence, which were analyzed by clinical experts in pediatrics, pediatric endocrinology, genetics and clinical laboratory in a virtual round of review. After adjusting the document, a second virtual round was required to approve the content of the document with the final recommendations. Subsequently, the recommendations were formulated, supported by the consulted evidence, and then were analyzed by clinical experts in pediatrics, pediatric endocrinology, genetics and clinical laboratory in a virtual round of review. After adjusting the document, a second virtual round was required to approve the content of the document with the final recommendations.

Information search

The search for CPG was performed on the following sites that compile and develop these types of documents: Ministry of Health and Social Protection (MSPS) of Colombia, GuíaSalud Spain, Guidelines International Network, CPG Infobase Canada, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, New Zealand Guidelines Group, Ministry of Health of Chile, National Center of Technological Excellence in Health of Mexico (*Centro Nacional de Excelencia Tecnológica en Salud de Mexico*, World Health Organization (WHO) and European Society of Pediatric Endocrinology; the terms *growth, short stature, turner, Prader, small for gestational age, chronic kidney disease* and *clinical practice guideline*, were used for this search, in English or in Spanish, depending on the search site.

We also consulted the medical database Ovid MEDLINE and the Google portal to expand the search of CPG on PWS and CKD using the terms *Prader Willi, chronic kidney disease, growth hormone* and *guidelines.*

In total, 149 articles were identified, of which five[22-26] were selected because they met the selection criteria (evidence-based CPG, addressed to the population under 18 years of age and published in the last 10 years in English or Spanish).

Five agencies for health technology assessments were consulted: Institute of Health Technology Assessment in Colombia (*Instituto de Evaluación Tecnológica en Salud de Colombia*), Health Technology Assessment Network of the Americas

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(*Red de Evaluación de Tecnología en Salud de las Américas*), Spanish Network of Health Technology Assessment Agencies and Benefits of the National Health System (*Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud*), Canadian Agency for Drugs and Technologies in Health and National Institute for Health Research) using the terms *growth hormone* or *somatropin* and their equivalents in Spanish, and 41 documents were identified, of which six were selected[12,13,27-30] because they met the selection criteria (being an evaluation of health technology aimed at a population under 18 years of age, having been published in the last 10 years in English or Spanish and having not been referenced in a more recent health technology assessment).

Subsequently, a non-systematic review of the literature was conducted in the PubMed and Cochrane databases to expand the information on biochemical diagnostic tests, genetic tests and pharmacological management in SS patients with specific diseases and health conditions: TS, PWS, CKD and SGA; the terms *growth, child, turner syndrome, Prader Willi syndrome, chronic kidney disease, mineral and bone disorder, small for gestational age, growth hormone, somatropin, pharmacological tests, stimulation tests, provocative testing*, in articles in English and Spanish, without date limit. The inclusion criteria were: studies in children under 18 years of age on pathologies approved in Colombia for treatment with somatropin.

The searches were conducted between April and September of 2019 and outcomes analyzed with more interest corresponded to diagnostic methods, treatment, safety, efficacy, adverse events, growth and body composition outcomes, final height achieved and other outcomes related to the use of somatropin.

Results

The derived recommendations for each or the 22 questions prioritized by the experts are presented below.

Question 1. What is the definition of SS proposed for Colombia?

SS is defined as a height below -2 standard deviations (SD) or of 2.3 percentile for chronological age and sex of a given patient, and ideally of the same ethnic or racial group.[31-34] It also corresponds to a height that, even though it is between ± 2 SD for the general population, is below the growth lane corresponding to the genetic height.

The literature has defined SS based on the mid-parental height when the patient is between 1 and 1.8 SD below it.[32,34] As there is no unit of auxological criteria in the publications, the recommendation for the Colombian population is to consider SS for mid-parental height when the patient grows at -1 SD ± 5 cm from it. Severe short stature would be the one below -3SD.[31,35]

Question 2. What is the classification of SS proposed for Colombia?

Given the characteristics of the Colombian population and considering the multiple classifications available for SS, the classification proposal is presented in Annex 2, which integrates concepts from the version of the European Society of Pediatric Endocrinology,[36] the one suggested in Argente, Spain[37,38] and the one proposed by Allen & Cuttler.[39]

Question 3. What criteria generate high suspicion to consider that a patient with SS requires treatment with somatropin?

There are pathologies whose auxological outcome is SS, but not all are susceptible to treatment with somatropin, therefore it is considered that the following characteristics merit further studies in order to establish a possible pharmacological treatment in this type of patients.[7,40-42]

- Having SS according to the definition proposed in these recommendations.
- Presenting pathological bone age delay.[43]
- Evidencing alteration in the grow rate (GR) with respect to the height percentile lane (usually -1

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SD) for age and sex documented in periods of at least 6 months and for a cumulative time of 2 to 3 years, or in general, when the GR has deteriorated significantly, even before reaching -2.5 SD.[33]

- Having in the medical history data compatible with the indications for the use of somatropin (dynamic tests suggestive of GHD, karyotype compatible with TS, history of SGA newborn, morbid obesity accompanied by cognitive deficit, pathognomonic phenotypic characteristics and CKD).

- Having ruled out the presence of other causes of SS (genetic, nutritional, organic, metabolic or psychogenic) not susceptible to treatment with somatropin.

Question 4. What are the criteria for referring a patient with SS from pediatrics to pediatric endocrinology?

The pediatrician must refer the patient to the pediatric endocrinologist when:

- A GR below the 25th percentile (or -1 SD) is documented in whom a specific cause of the SS is not detected.[22]

- Being in front of a patient with a history of being born SGA who does not show height recovery at two years of age and in whom no specific cause is detected.[22,44]

- The patient has SS with high weight for height in the range of overweight or obesity and hypothyroidism, glucocorticoid excess or GHD are suspected.[22]

- Discordance between chronological age and sexual maturity according to Tanner stages is detected. [22]

- Delayed bone age is detected and hypothyroidism is suspected in children with postnatal SS. [22]

- Any of the following pathologies is suspected or identified: GHD; dysfunction in the secretion of somatropin secondary to radiotherapy; CKD in conservative treatment, dialysis or hemodialysis; pre and post kidney transplantation; TS; dysmorphism or disproportionate SS, and suspected chromosomal abnormality.[22]

The referral to pediatric endocrinology of patients who grow by their genetic lane, whose target height is included in the population reference and who also have a good GR is not considered a good clinical practice.

Question 5. What are the cut-off points for growth hormone stimulation tests?

The literature refers different cut-off points for growth hormone that vary according to the population studied, as well as in the case of patients diagnosed with obesity and overweight,[45] and according to the methodology used in the laboratory.[46-52] In Colombia there is no information to define or establish these cut-off points, thereby Table 1 presents some studies that report values for the determination of adequate plasma levels of growth hormone that differ according to the type of stimulation test used and the standardization of tests at the local level.

Question 6. What is the usefulness of determining the insulin-like growth factor 1 (IGF-1) in children with SS?

The determination of IGF-1 is a diagnostic aid and a follow-up criterion, since the low values suggest GHD and their elevation during the treatment with growth hormone allows to evaluate the response.[53] However, for children between 3 and 8 years it is recommended to be cautious with the request of this exam and the interpretation of the results, since the values that are considered normal can overlap between patients with an without GHD.[53,54]

In patients under treatment with somatropin, it is suggested to monitor IGF1 levels twice a year and to especially monitor patients with high determinations. Likewise, various authors recommend titrating the dose of this hormone based on the IGF-1 values.[23,25,55]

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Table 1. Cut-off points of growth hormone published in some studies.

Year	Country	Cut-off point	Assay	Reference
1996	Italy	10 µg/l	RIA	47
2006	Argentina	5.4 µg/l	IQL	48
2014	Germany	7.09 µg/l	IQL	49
2016	Brazil	3 µg/l	IQL	50
2016	United Kingdom	6-8 µg/l	IQL	51
2019	Brazil	7 µg/l	IQL	52

RIA: radioimmuunoasay; IQL: immunochemiluminescence. Source: Own elaboration.

Question 7. What reference values of IGF1 are suggested to be used in Colombia?

In Colombia there are no reference values for IGF-1 and these are linked to the platform (equipment) and the processing technique; for this reason, the results may vary between each laboratory. There are different reference values in the literature that can be consulted by the pediatric endocrinologists,[56-59] but given the national panorama it is important that professionals know in which processing platform the test was performed in order to correlate the results with the information available.

Some authors suggest that IGF-1 values vary depending on the age, gender and pubertal development stage, so there are tables that show reference values according to Tanner 's stage of pubertal development.[58,60] Likewise, the results can also be analyzed according to the SD (Z-score) of the reference population for each test and whose values are distributed between +2 SD (97.5 percentile) and -2 SD (2.5 percentile).

Question 8. What somatropin stimulation tests should be requested when GHD is suspected?

It is suggested that dynamic tests with chemical stimulation for the diagnosis of GHD are requested by the pediatric endocrinologist as a last-line study to confirm this diagnosis, the above taking into account that the results are not the single criterion to define the pharmacological treatment and that two dynamic tests with different stimuli are required to confirm GHD following standardized laboratory protocols.[25,52]

The performance of dynamic test implies the compliance with technical requirements, infrastructure and standardized processes, as it implies the administration of drugs with potential risk for the safety of the patient; in this sense, medical surveillance becomes necessary in a service center with the capacity of initial care for possible adverse effects, and hospitalization in cases of difficult management.

Based on the foregoing, in Colombia it is considered a good clinical practice to request the dynamic tests available in the laboratories authorized lin the country with the stimuli of clonidine, insulin, glucagon and levodopa.[8,33,52,61-69]

Question 9. What are the indications for testosterone or estrogen impregnation?

It is the duty of the clinician to make the decision to formulate impregnation with sex steroids before the requested functional tests when GHD is suspected in prepubescent boys >11 years and in prepubescent girls >10 years to prevent unnecessary treatment with somatropin in children with constitutional delay of growth and development.

Regardless of gender, it is recommended to indicate 2 mg of β-estradiol (1 mg for a body weight <20 kg) orally during the two nights before the test. Males can be prepared with intramuscular testoste-

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rone (50-100 mg of a depot formulation administered one week before the test).[25]

Since the availability of sex steroids for impregnation is not constant in some countries, it is suggested to individualize the decision to perform dynamic tests in this way.

Question 10. In which population and with what frequency is indicated to determine the bone age?

It is necessary to determine the bone age through an anteroposterior radiograph of the left hand and wrist (carpogram) in children > 3 years of age in whom an alteration of the GR has been documented[43,46,70,71]; this test is not recommended in children <2 years, in whom the assessment of the bone age is less reliable. In the same way, it is recommended to take special care in obese children, in whom the bone age is typically advanced.[54] There is no certainty about when it should be repeated or perform radiological follow-up, but it is recommended to evaluate the benefit of its performance given the levels of exposure to ionizing radiation to which a child may be subjected in the case of indiscriminately repeating the study.

In general, it is suggested to consider to take a carpogram annually in patients who are being treated with somatropin; in specific conditions such as pubertal development, it may be taken at shorter intervals according to the criterion of the treating physician.

Question 11. What is the dose of somatropin according to the indications approved in Colombia?

In Table 2 are listed the doses of somatropin according to the indications approved so far in Colombia. The literature suggests to titrate the dose based on the IGF-1 values.[23,25,55]

Question 12. What are the molecules and technical specifications of the somatropin most commonly used in Colombia?

In Colombia there are several molecules of somatropin with INVIMA registry, but the most frequently used are listed in Annex 1, along with their technical specifications.

Question 13. What growth curves are suggested to be used in Colombia for the follow-up of children with SS?

It is suggested to follow the recommendations of the CPG of growth and development of the MSPS of Colombia,[74] where two main recommendations are made:

- Use the indicator height-for-age below -2 SD for their age and sex in the growth reference patterns of the WHO to classify children between 0 and 5 years of age as SS for age (delay in height).[74]

Table 2. Growth hormone dose according to the indications approved in Colombia.

Therapeutic indication	Dose µg/kg/day	Dose mg/kg/day	Dose IU/kg/day*	Reference
Growth hormone deficiency	22-35	0.023-0.034	0.07-0.1	25
Turner syndrome	45-50	0.045-0.05	0.14-0.15	23
Prader-Willi syndrome**	35	0.017-0.035	0.05-0.1	24
Chronic kidney disease in <18 years	45-50	0.045-0.05	0.14-0.15	26
Small for gestational age newborn without catch-up growth	35-70	0.035-0.07	0.1-0.2	13.72

* 1 mg of somatropin corresponds to 3IU of somatropin.
** Bakker *et al.*[73] suggest 1 mg/m^2/day of somatropin as a dose for patients with Prader Willi syndrome.
Source: Own elaboration.

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- Use the indicator height-for-age below -2 SD for their age and sex in the Colombian growth curves to classify children between 5 and 10 years of age as SS-for-age (delay in height).[74]

For the clinical diagnosis and follow-up of patients with SS, it is proposed to compare the auxological parameters (height, weight, body mass index and head circumference) with those generated from the Colombian population between 0 and 20 years of age and published by Durán *et al*.[75] in 2015, since the growth dynamics and the final height depend mainly on the genetic load and take into account the substantial effect of the specific environmental factors of each population.

Regarding the GR, it should be considered that while local curves are generated, we must use the reference patterns of the study conducted by Kelly *et al*.[76] published in 2014, which demonstrated statistical superiority compared to those proposed by Tanner & Whitehouse,[77] that were developed with the statistical technique of centralization that can oversize the GR and had an evident bias in the selection of the population for their development. The study by Kelly *et al*.,[76] conducted with the Lambda Mu-Sigma (LMS) mathematical method for the adjustment of anthropometric data, also included Latin population and considered slow, average and rapid maturation profiles.

Question 14. What codes of the 10th edition of the International Classification of Diseases (ICD-10) should be used in Colombia for the unified registry of health conditions related to SS in children?

For the unified registry of health conditions related to SS in children, it is suggested to use the ICD-10 codes presented in Table 3.

It is suggested to use the code E230: hypopituitarism in patients in whom growth hormone deficiency has been confirmed. The R629 code will be used in the patient with short stature on etiological study.

Question 15. What are the criteria for suspension or withdrawal of somatropin?

The decision to interrupt the treatment with somatropin should be made in conjunction with the patient and/or the caregivers, when the epiphyseal

Table 3. Main ICD-10 codes related to short stature in children.

Name of the pathology or health condition		ICD-10 code
Short stature, not classified	**Includes:** NOS (Not otherwise specified) constitutional short stature, Laron-type short stature, psychosocial.	**E34.3**
	Excludes: other specific endocrine disorders (E34.8), congenital malformation syndromes mainly associated with short stature (Q87.1), Immunodeficiency with short-limb dwarfism (D82.2), achondroplastic (Q77.4), delayed development followed by protein and energy malnutrition (E45), hypopituitarism (E23.0), renal osteodystrophy (N25.0)	
Hypopituitarism		**E23.0**
Small for gestational age		**P05.1**
Congenital malformation syndromes mainly associated with short stature		**Q87.1**
Turner syndrome, unspecified		**Q96.9**
Lack of expected normal physiological development, unspecified		**R62.9**
Chronic renal failure, unspecified		**N18.9**

Source: Own elaboration.

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closure is demonstrated[26]; when the patient is within the genetic range of target height and has a GR <2 cm of total growth in one year,[13] and when there are insuperable problems of adherence to treatment.[13] It should also be discontinued in patients with bone age >16 years when they are boys and >15 when they are girls.

Having reached a high within the range of the family height calculated according to Tanner's formula[78,79] should also be considered as an event to interrupt treatment. Somatropin should be discontinued in patients with CKD and persistent severe secondary hyperparathyroidism (Parathyroid hormone [PTH] > 500 pg/ml), but it can be re-established when the levels return to the desired target range of PTH.[26] This treatment should also be discontinued when any serious adverse event appears (avascular necrosis of the femoral head or epiphysiolysis of the femoral head)[26] and/or reported in the technical data sheet of the drug. (See Annex 1). Finally, if the patient does not respond adequately to treatment despite optimal nutritional and metabolic control, it should be postponed.[26,80]

Question 16. Is the use of an Informed Consent to start treatment with somatropin suggested in Colombia?

It is suggested that informed consent is part of the medical history of the patient as a document that evidences the process of participation in making informed decisions by the patient and their caregivers, both to accept and to reject the initiation of treatment (Annexes 3 and 4).

Question 17. What are the considerations related to the use of somatropin in patients with and without GHD?

According to the CPG of *Grimberg et al.*,[25] the following considerations are proposed regarding the use of somatropin in patients with or without GHD:

- The diagnosis of GHD does not require provocation tests when the following three conditions are met: auxological criteria, some hypothalamic-pituitary defect (malformation, neoplasm or radiation) and deficiency of at least one additional pituitary hormone.[25]

- GHD due to congenital hypopituitarism does not require somatropin provocation tests in a newborn with hypoglycemia who does not reach a serum concentration of this hormone above 5 µg/L and has a deficiency of at least one additional pituitary hormone and/or the classic imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stem).[25]

- Given the substantial number of healthy children with normal growth and tests below the accepted limits, an inadequate response to two provocation tests with different stimuli is required for the diagnosis of GHD.[25]

- Given the big discrepancies between trials with somatropin, it is recommended that institutions request that laboratories provide harmonized trials on this hormone using the standard (IRP IS 98/574, 22k rhGH isoform) as recommended by the consensus statements of 2006 and 2011 and the published commutability standards.[25,81]

- It is not useful to request basal growth hormone levels to confirm the diagnosis of GHD in a clinical setting,[25] so dynamic tests are used for this purpose.

- In Colombia it is no necessary to carry out dynamic tests for other approved indications for the use of somatropin (other than GHD), whenever they are documented with the respective studies for each diagnosis (TS, PWS, CKD, SGA).[23,24,26,82]

- It is recommendable to perform a nuclear magnetic resonance imaging with contrast of the sella turcica and the suprasellar region, once the diagnosis of GHD is confirmed and before starting treatment with somatropin,[34] as well as to evaluate the other pituitary hormones.

- The adrenal and thyroid axes should be reassessed after initiation of the therapy with somatropin in patients whose GHD is associated

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with possible multiple pituitary hormone deficiencies (panhypopituitarism).[25]

- Some conditions have an increased intrinsic risk of malignancy (neurofibromatosis-1, Down syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome and Diamond-Blackfan anemia), and therefore the prescription of somatropin is not recommended in these patients.[25]

Question 18. What are the considerations related to the use of somatropin in patients with TS?

According with the CPG of Gravholt *et al*.[23] the following considerations are proposed:

- It is recommended to make a kariotype to every girl who has come to supra-specialized consultation (pediatric endocrinology or genetics) for SS without an apparent cause).[23]
- In women with TS, somatropin treatment should be started early (around 4 to 6 years of age), when there is evidence of a decrease in GR below the 50th percentile and sustained in this way for 6 months; in the absence of another treatable cause of growth deficit; when there is a high probability of SS due to parents with short stature or predicted adult SS, and when the patient is at a population age of puberty at the time of diagnosis of TS.[23]
- The treatment with somatropin should be monitored in women with TS by measuring height every 4-6 months during the first year of treatment and every 6 months thereafter.[23]
- The safety of somatropin therapy should be monitored by measuring IGF-1 at least once a year; if the values are above +3 SD of the mean for the age, a reduction of the dose of the hormone is justified, but for values between +2

  SD and +3 SD, clinical judgment should guide the selection of the dose.[23]
- Screening for hypothyroidism should be performed at the time of diagnosis and then annually with measurements of free T4 and TSH

beginning in early childhood and during the whole life.[23]

- It is necessary to request an annual measurement of HbA1c lifelong with or without fasting glycemia. [23]
- Clinical evaluation for scoliosis every 6 months is recommended during somatropin therapy until growth is completed; if the evaluation is done in another way, it must be annual.[23]
- It is suggested not to add routinely very-low dose estrogen supplements in prepubertal patients to promote growth[23] and that pubertal induction with estrogens between 11 and 12 years of bone age is a mimetic effect of the pubertal growth spurt.[23]

Question 19. What are the considerations related to the use of somatropin in patients with PWS?

According to the CPG of Deal et al.[24] the following considerations are proposed:

- Patients with PWS must have a genetically confirmed diagnosis and a multidisciplinary clinical evaluation before initiating the treatment with somatropin. If it has been started, it should be continued as long as the benefits outweigh the risks.[24]
- Somatropin stimulation testing is not required as part of the therapeutic decision-making process in children with PWS.[24]
- Exclusion criteria for the initiation of somatropin treatment in patients with PWS are morbid obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis.[24]
- Scoliosis is not an absolute contraindication, but is a relative contraindication for the treatment with somatropin in patients with PWS. Therefore, strict follow-up must be carried out because the disease may worsen during treatment.[24]

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- The treatment with somatropin should be carried out in the context of appropriate dietary, environmental, and lifestyle interventions for the care of all patients with PWS.[24]

- Cognitive impairment should not be a barrier to treatment with somatropin in patients with PWS.[24]

- IGF-1 levels in patients with PWS under treatment with somatropin can be kept within the upper limit of the normal range (maximum + 2SD),[24] this taking into account that immunoreactive IGF-1 levels do not represent the bioactive IGF-1 levels in children with PWS treated with the hormone. Therefore, increased levels are not an indication of overdose.[73]

- Patients with PWS who receive somatropin should be closely monitored for possible adverse effects of treatment every 3 to 6 months.[24]

Question 20. What are the considerations related to the use of somatropin in patients with CKD?

- Patients with CKD and treatment with somatropin should be interdisciplinary evaluated by pediatric nephrology and endocrinology, because although the pediatric nephrologist could initiate treatment in appropriately selected patients, the pediatric endocrinologist should be in charge of it, ideally from the beginning, and be the responsible for the follow-up.

On the other hand, in accordance with the consensus of Drube *et al*.[26] and with the recommendations from a group of local experts, based on scientific evidence (data to be published), the following considerations are proposed:

- Age, assessment of the pubertal status according to Tanner's scale, eye fundus, etiology of the renal disease, systemic disorders, stage of the CKD, adequation or the dialysis (for patients on dialysis), time of transplantation and degree of graft function, and glucocorticoid therapy (in post-transplant children), the latter given that high doses of glucocorticoids can almost completely suppress the effect of the hormone, should be taken into account for the initiation of treatment with somatropin.[26]

- The efficacy of treatment in properly selected patients will be greater if the therapy is started before puberty and before the deterioration in height is marked.

- Growth-limiting factors associated with CKD, such as protein-calorie malnutrition, metabolic acidosis, electrolyte disorders (hyponatremia), dehydration, and bone mineral disease, including secondary hyperparathyroidism should be controlled before starting therapy with somatropin.[26]

- Evidence suggests that treatment with somatropin increases height in patients with CKD, being higher if it is started before dialysis, less if it is started during it, and intermediate if it is started post-transplant. The treatment is safe from the point of view of the intervention and the kidney disease itself.

- When starting treatment, is important to carry out an auxological assessment, of pubertal development, bone maturation, bone mineral density, lipid profile, glucose, HbA1c, insulin, IGF-1, serum creatinine, estimated glomerular filtration rate, urea, calcium, phosphorus, total alkaline phosphatase, bicarbonate, parathyroid hormone, 25(OH)-vitamin D and albumin.[26]

- In children post-renal transplant, somatropin therapy should be started one year after transplantation if the growth recovery is not spontaneous and immunosuppression without steroids is not feasible.[26]

- Somatropin therapy should be considered in patients with CKD at any stage, because due to the nephropathic cystinosis they present a persistent growth failure despite adequate treatment for this condition.[26]

- In a patient with advanced CKD and treatment with somatropin, quarterly/six-monthly controls

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should be performed to monitor height, GR, pubertal development, renal function, and levels of TSH, free T3, glycemia, calcium, phosphate, bicarbonate, and parathyroid hormone.[26]

- If the GR in the first year of treatment with somatropin is less than 2 cm per year above the baseline, the adherence of the patient to treatment, including the measurement of serum IGF-1 levels, dose of somatropin adjusted to the weight and assessment of nutritional and metabolic factors should be evaluated.[26]

- Somatropin should be discontinued at the time of kidney transplantation, in case of an unexplained decrease in the estimated glomerular filtration rate,[26] in cases of onset of significant proteinuria not explained by recurrence of the primary disease in the graft,[83] in suspicion of malignancy, when the goal has been reached based on the midparental height or 50th percentile for age and when there is epiphyseal closure, displacement of the femoral epiphysis and intracranial hypertension.

Question 21. What are the considerations related to the use of somatropin in SGA children?

By definition, a newborn is SGA when it is born with weight, length and/or head circumference below -2 SD for the weeks of gestation and sex with respect to the standards published in the INTERGROWTH 21st study.[84,85] In this sense, all patients who are or were SGA require an exhaustive study of the probable etiology that led them to this outcome in the first 2 years of life. In case that a specific cause is found, it should be treated or referred for treatment with the pertinent specialist.[82]

SGA children who do not have a growth recovery or height re-catching at 2 years of age require a new clinical evaluation to determine the cause. In case that it is not found or if a hormonal alteration is suspected, an evaluation by pediatric endocrinology for diagnosis and/or treatment is recommended.[44,82]

SGA children without height re-catching at 2 years of age in whom a specific cause of growth failure is not established and syndromic etiology other than the approved indications listed in this text is ruled out are candidates for treatment with somatropin.[44,82]

Likewise, in SGA patients, therapy should be monitored with the clinical and paraclinical parameters exposed in this document, and although there is no consensus about the safety levels of IGF-1, it is suggested to keep them during somatropin therapy within a limit between 1.5 and 2 SD for age and sex.[86]

Question 22. Which patients with SS require evaluation by a specialist in genetics?

An evaluation by clinical genetics is required when a patient presents SS associated with neurodevelopmental delay or cognitive deficit, alteration in body proportions, facial dysmorphism, multiple congenital malformations (understood as two or more affected organs or systems) and/or characteristics that are consistent with a specific syndromic association such as Noonan syndrome, TS, PWS.) In these patients, the cytogenetic or molecular analysis can help determine the cause of the SS and/or the condition of the patient, and may even establish the need to study the parents or other relatives, all this with adequate genetic counseling that allows to determine the risks of recurrence and a timely prenatal diagnosis in future generations.[38,87,88]

Genetic and/or epigenetic tests are not necessary for all children with SS, but they should be used in the diagnostic evaluation of specific groups of children whose phenotype suggests a high probability of a genetic cause such as isolated GHDs, familial SS, specific syndromes with multiple pituitary deficiencies, severe SS (<-3 SD of the population more than 3 SD below their midparental height), body disproportion and/or skeletal dysplasias; they should also be practiced in SGA children without adequate growth recovery.[54]

Conclusion

Somatropin is a drug frequently used in the practice of the pediatric endocrinologist. There are specific

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criteria and doses for its use, as well as diagnostic tests and follow-up, depending on the indication for which it is prescribed. Answering the questions that generate uncertainty in clinical practice allows establishing a unit of criteria at the national level that will generate an impact on the statistical record, research work, clinical follow-up and rational use of resources in the health system, based on the best available evidence and expert agreement in the context of professional practice in Colombia.

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Conflict of interest

There were no conflicts of any nature for the development of this study. All the authors attached and signed their respective conflict of interest document.

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Ethical responsibilities

Each of the authors, through their academic contributions, responded to the ethical consideration to unify the criteria in clinical practice, with social responsibility, and the aim of improving the hormonal health conditions of Colombian children.

Contribution of the authors

We certify that we have contributed with the scientific and intellectual material, data analysis and writing of the manuscript, taking responsibility for its content. We have not conferred any right or interest in the work to third parties. We also certify that all figures and illustrations that accompany this work have not been digitally altered and faithfully represent the reported facts.

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Annex 1. Technical data sheet of the drug somatropin.

1. Available presentations and pharmaceutical forms:

Brand name	Presentation	Concentration	Device	Laboratory	Pharmaceutical form
Genotropin®	5.3 mg	5.3 mg (16 IU)	Pen 0.1 mg per click	Pfizer	Powder
Genotropin®	12 mg	12 mg (36 IU)	Pen 0.2 mg per click	Pfizer	Powder
Saizen®	6 mg/mL	5.83 mg/mL (15 IU)	Easypod	Merck	Liquid
Saizen®	20 mg/2.5 mL	8 mg/mL (26.4 IU)	Easypod	Merck	Liquid
Norditropin®	5 mg/1.5 mL	3.33 mg/mL→10 IU 5 mg → 15 IU	Pre-filled pen	Novo Nordisk	Liquid
Norditropin®	10 mg/1.5 mL	6.7 mg/mL → 20 IU 10 mg → 30 IU	Pre-filled pen	Novo Nordisk	Liquid
Norditropin®	15 mg/1.5 mL	10 mg/mL →30 IU 15 mg →45 IU	Pre-filled pen	Novo Nordisk	Liquid
Omnitrope®	10 mg/1.5 mL	6.7 mg/mL → 20 IU 10 mg → 30 IU	Surepal 10	Sandoz GMBH	Liquid
Omnitrope®	15 mg/1.5 mL	10 mg/mL ◊ 30 IU 15 mg ◊ 45 IU	Surepal 15	Sandoz GMBH	Liquid

Source: Own elaboration.

For other molecules of somatropin available in Colombia consult the INVIMA website.

2. Therapeutic indications:

Somatropin is approved in Colombia for the treatment of the following growth disorders in children and adolescents and its dosage must be adapted to the needs of each child and the type of condition to be treated:

Brand name	Growth hormone deficiency	Turner syndrome	Prader Willi syndrome	Chronic renal failure	Born small for age gestational without catch-up growth after 4-5 years
Genotropin® (Pfizer)	X	X	X	X	X
Saizen® (Merck)	X	X	-	X	X
Norditropin® (Novo nordisk)	X	X	-	X	X
Omnitrope® (Sandoz)	X	X	X	X	X

Source: Own elaboration.

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3. Administration:

The administration of somatropin can be subcutaneous (arm, abdomen, buttocks or thighs with rotation of the injection sites to avoid lipoatrophy) and should be administered between 7 and 8 o'clock at night, 6 to 7 times a week.

4. Contraindications:

Known contraindications for somatropin are:

- Hypersensitivity to excipients.
- Postoperative of major surgery (heart, abdomen, multiple trauma)
- Acute respiratory failure due to increased mortality risk
- Active malignancy
- Pediatric patients with closed epiphyses.
- Active non-proliferative diabetic retinopathy.
- Patients with Prader-Willi syndrome and severe obesity, sleep apnea, airway obstruction, or severe respiratory failure.

5. Adverse reactions:

The adverse reactions of somatropin are classified into:

- *Frequent* (<10%): these reactions include edema, rash, arthralgia, myalgia, headache, rhinitis and paresthesias.
- *Very rare*: these reactions include epiphyseal slippage or avascular necrosis of the femoral head, hypothyroidism, hyperglycemia, nausea, scoliosis, tumor relapse in patients with a history of neoplasia, apnea in patients with Prader-Willi syndrome, hematuria, pancreatitis, infections, hypertension and anaphylaxis.

6. Pharmacological interactions:

The drug interactions of somatropin occur with glucocorticoids, anticonvulsants, cyclosporins, oral estrogens, insulin, and oral hypoglycemic agents.

7. Overdose and toxicological data:

In cases of severe toxicity, somatropin should be discontinued for up to 5 days, then restarted at a 50% dose; If severe toxicity recurs or does not disappear within 5 days, treatment should be stopped, as it causes hypoglycemia and hyperglycemia in the short term and can cause acromegaly in the long term. Similarly, it is likely to cause fluid retention.

8. Pharmacodynamic properties:

Mechanism of action: Somatropin binds to a dimeric receptor on the cell membrane of target cells, resulting in intracellular signal transduction. Some pharmacodynamic effects are mediated by the level of IGF-1 produced in the liver and locally (skeletal growth and protein synthesis), while others are a consequence of the direct effects of the hormone (lipolysis). In this way, somatropin stimulates tissue growth, linear growth (height), and the metabolism of proteins, carbohydrates, lipids, and minerals.

9. Pharmacokinetic properties:

Absorption: somatropin by subcutaneous route has a bioavailability >70%. A subcutaneous dose of 0.035 mg/kg produces plasma Cmax and tmax values in the range of 13-35 ng/mL in 3 and 6 hours, respectively. The absorption velocity is affected by the site of administration, subcutaneous blood flow, muscle activity, the volume and concentration of the drug injected, the depth of injection (onset of action faster intramuscularly than subcutaneously) and body temperature (the increase in temperature produces vasodilation and decreases the viscosity, increasing the solubility of the drug; the opposite effect is achieved by applying cold).

Distribution: the volume of distribution of somatropin can be higher than 1.3 L/kg, being reported values of 12 L in some presentations.

Metabolism: Somatropin works through hepatic metabolism.

Elimination: elimination of somatropin occurs through renal route. After subcutaneous administration,

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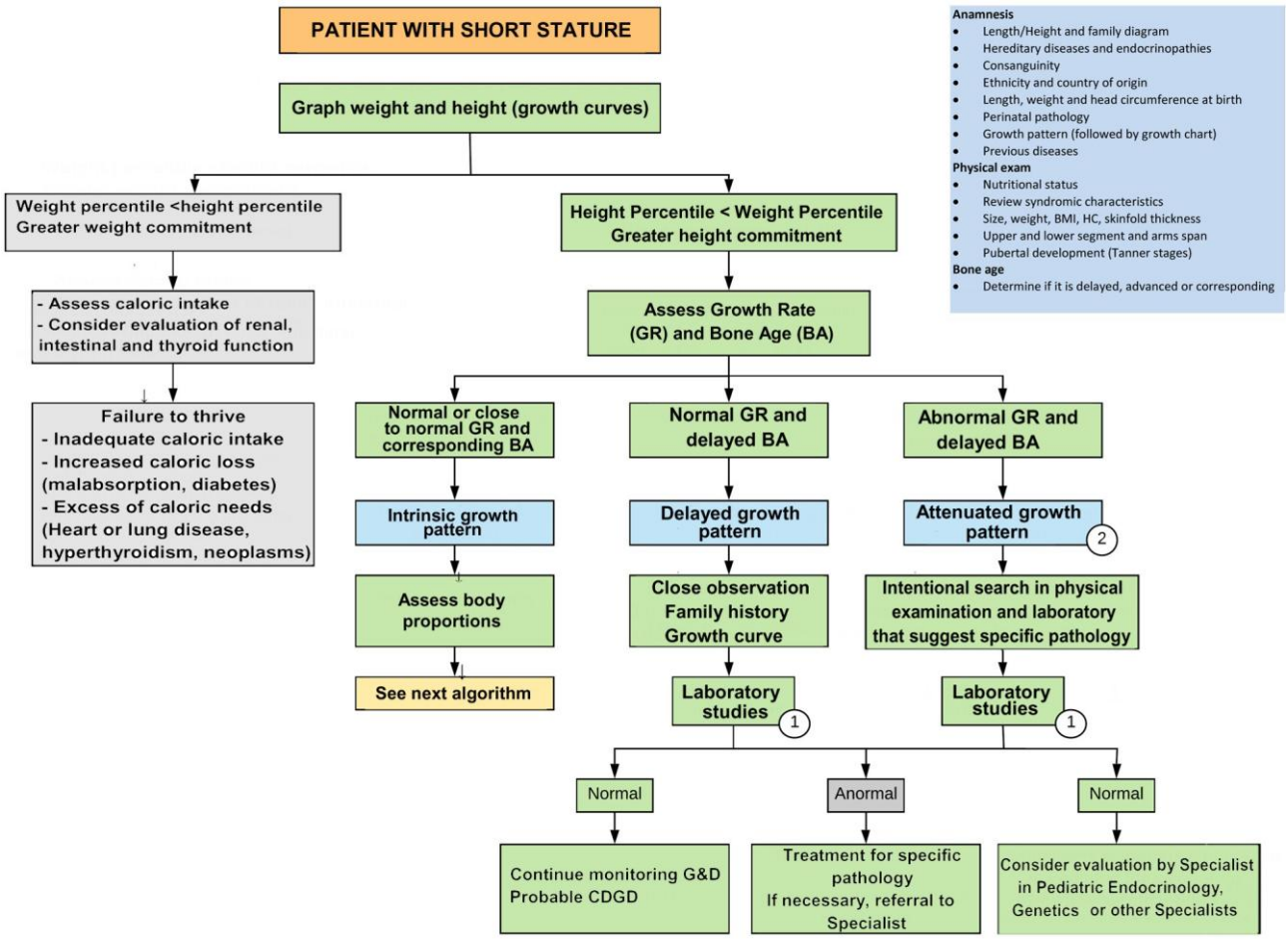
half-lives of 2-3 hours are achieved, although the half-life ($t_{1/2}$) in plasma is short, its biological $t_{1/2}$ is considerably longer, and once-daily administration is sufficient.

10. Considerations for the use of the drug:

- Before administering somatropin it should be verified that the solution for injection should is clear.
- The drug should be kept refrigerated (2-8ºC), but not frozen, and protected from light.
- The stability of the drug molecule varies according to the reference laboratory, for which the specifications of the molecule according to the trading firm must be reviewed.

Anexo 2. Algoritmo propuesto para la clasificación de talla baja.



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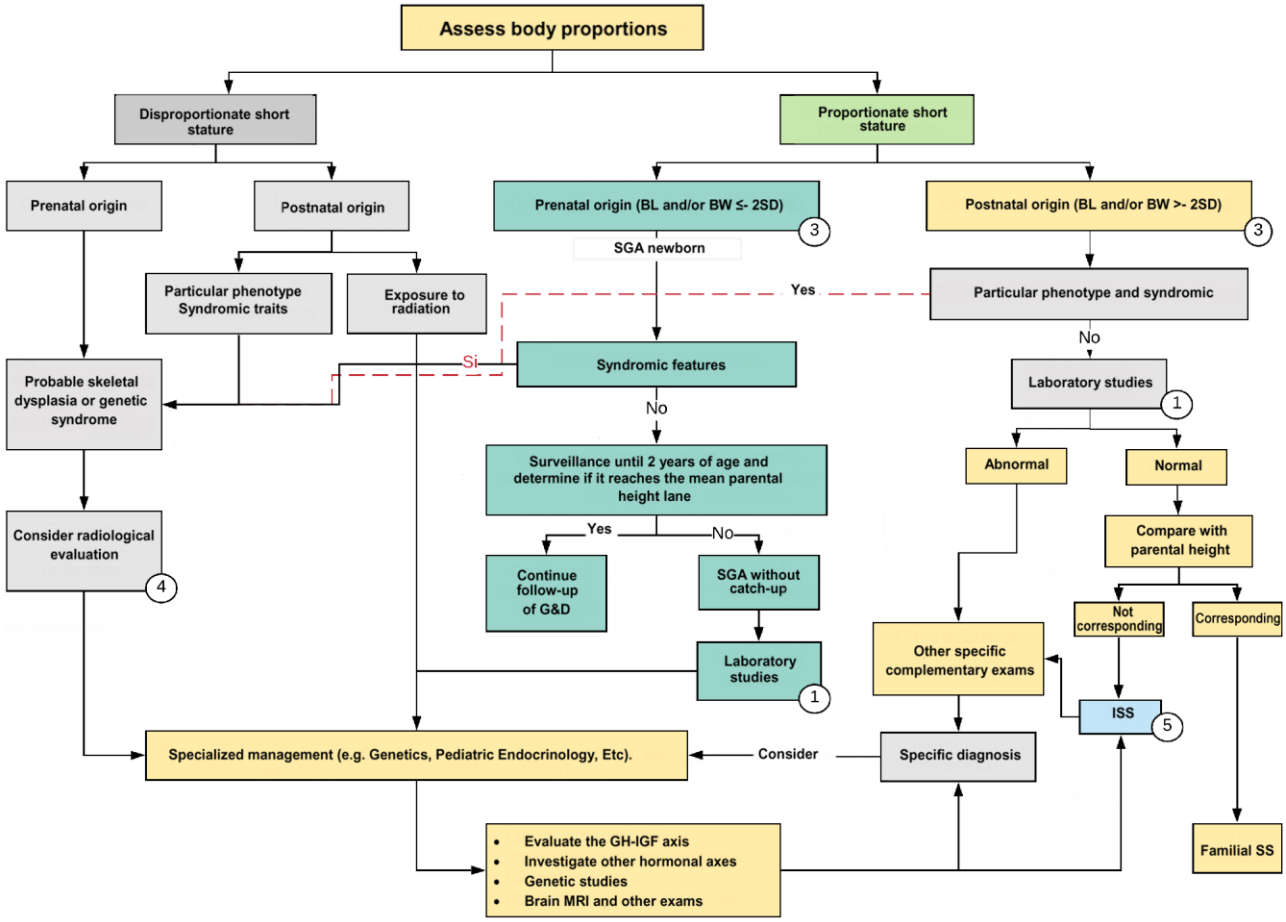

BL: birth length; BW: birth weight; SD: Standard deviation; SGA: small for gestational age; SS: short stature; ISS: idiopathic short stature; GR: growth rate; BA: bone age; GH: growth hormone; G&D: growth and development; CDGD: constitutional delay of growth and development.

Annexes of the numeration contained in the Algorithm:

1. Laboratory studies: Complete blood count, ferritin, CRP, ESR, BUN, creatinine, transaminases, alkaline phosphatase, ionogram, venous gases in <3 years of age, urinalysis, TSH, free T4, IGF-1 and karyotype in all girls. IgA anti-transglutaminase antibodies if celiac disease is suspected.

2. ALERT: It is always a pathological growth pattern and a disease must be ruled out.

3. Using the reference parameters of INTERGROWTH 21.

4. Radiological studies should be performed and, according to semiology, refer to genetics to evaluate the relevance of carrying out specialized studies in the event of suspected congenital skeletal dysplasias (*achondroplasia, hypochondroplasia, multiple epiphyseal dysplasias, RASopathies, among others*). Likewise, identify children with disproportionate acquired TB secondary to malformations, radiotherapy, tumors, and other diseases.

5. Among the causes of short stature of unknown etiology, is idiopathic short stature (ISS). In general, ISS patients have normal weight at birth and GH sufficiency. If there is no specific diagnosis and the short stature is severe or has a familial component, referral to the geneticist should be considered for evaluation of the need for an exome study.

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Annex 3. Informed consent for initiation of treatment with somatropin

INFORMED CONSENT FOR THE USE OF SOMATROPIN IN PEDIATRIC PATIENTS

Mr(s) father (mother) of family and/or guardian:

Taking into account that, according to the medical diagnosis, your child has one of the approved indications for the use of growth hormone in Colombia, below you will find information about the medication offered for this purpose. This information will allow you to clear up any doubts about the treatment and authorize it, which will contribute to its success.

What is growth hormone?

Growth hormone is a substance produced by the pituitary gland that is responsible for regulating the growth of the body, helping to increase height and muscle mass, and decrease body fat. This hormone also helps control the body's metabolism, which is the process by which cells convert food into energy and produce other substances that the body needs. When there is a medical condition that requires the administration of growth hormone, replacement therapy is performed with the synthetic form of the hormone (also called somatropin), which is not covered by the Health Benefits Plan, as it is considered a high-cost medicine and the approval of its administration is done through the MIPRES platform of the Ministry of Health and Social Protection.

What are the indications approved in Colombia for its use?

1. Growth hormone deficiency
2. Turner syndrome
3. Prader-Willi syndrome
4. Chronic kidney disease in children under 18 years of age
5. Children born small for gestational age without catch-up growth

In which cases is the use of growth hormone not approved in Colombia?

1. Family short stature
2. Idiopathic short stature (of unknown cause)
3. Short stature of other syndromic origins (Noonan, Silver Russell, Down, etc.)
4. SHOX gene mutation
5. Cystic fibrosis
6. Congenital adrenal hyperplasia
7. Severe burns
8. Juvenile rheumatoid arthritis
9. Short bowel syndrome
10. Achondroplasia and hypochondroplasia

How is growth hormone administered?

The drug is given as subcutaneous injections (under the skin) once a day, at bedtime and ideally no later than 8:00 p.m., 6 to 7 times a week. It can be applied at home, and even older children can learn how to inject themselves. As it is a biological medicine, it requires refrigeration, and freezing of the product should be avoided (take this into account for transport and storage). This information will be expanded in the respective training for its application.

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The attending physician will decide the dose, frequency and presentation of the medicine to be administered based on the diagnosis, weight or body surface of your child. The application of the drug requires training for which you will be contacted at the time of the first delivery. Follow the indicated instructions for administration exactly.

What are the benefits of treatment with growth hormone?

According to the medical indication for which the drug is prescribed for your child, benefits are expected that will be widely explained by the treating physician and that not only involve the recovery of height but also changes in body composition (normalization of muscle mass and bone) and decreased cardiovascular risk. According to the medical indication for which the drug is prescribed for your child, benefits are expected that will be widely explained by the treating physician and that not only involve the recovery of height but also changes in body composition (normalization of muscle and bone mass) and decreased cardiovascular risk. Regarding the height, the sooner the treatment is carried out, the greater the probability that your child will grow until reaching an adult height close to that expected according to the established therapeutic goals. During the first year of treatment, the highest growth rate is expected, which will slow down a little bit during the next 2 years. After this, the growth rate slowly decreases.

It must be borne in mind that the action and application of growth hormone therapy is daily and therefore strict adherence is required, not only to the application of the drug but also to the adjustments required in the determining factors of growth such as sleep hygiene, physical activity and healthy eating (free of processed food). Failure to follow these recommendations can lead to non-response to the action of the drug; therefore, the commitment of the entire family nucleus is required for the success of the treatment.

A small percentage of patients do not respond to treatment, so the impact should be evaluated in periodic controls, eventually requiring dose adjustment or drug withdrawal when it is considered that there has been no response to it.

What are the risks of treatment with growth hormone?

Adverse events are classified medically as common (affecting 1 to 10 out of 100 patients), uncommon (affecting 1 to 10 out of 1,000 patients), rare (affecting between 1 and 10 out of 10,000 patients), very rare (affecting 1 out of 100,000 patients), and of unknown frequency (frequency cannot be estimated from the available data). According to this classification, the adverse effects described with the use of somatropin are the following:

1. *Common adverse effects*: redness and itching at the injection site. If this is especially disturbing, you should discuss it with the attending physician.

2. *Uncommon adverse effects:* carpal tunnel syndrome, characterized by a persistent sensation of "electric shock", with a burning sensation, pain and/or numbness in the hand; headache (isolated): edema (swelling); muscle pain; and joint pain and disorders. These adverse effects usually appear at the beginning of treatment and are transitory (similar to "growing pains").

3. *Very rare adverse effects:* epiphyseal slipping of the femoral head (a problem in the hip that occurs if the growth cartilage of the femoral head shifts) and avascular necrosis of the femoral head (a pathological process in which cells that make up the head of the femur die when they do not receive enough blood

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supply). If your child has an unexplained lameness and hip or knee pain, you should discuss it with the attending physician. Reduction in thyroid hormone levels may also occur and, if necessary, appropriate treatment will be prescribed, which is generally transient during the use of growth hormone therapy.

4. *Unknown frequency:* headache, vision problems, malaise (nausea) and the urge to vomit, manifestations that may be symptoms of increased intracranial pressure. Hyperglycemia (high blood glucose levels), skin rash, breathing difficulty, swollen eyelids, face or lips, and syncope may also occur. Any of these symptoms may indicate an allergic reaction, so if they occur, the drug should be discontinued and you should consult the attending physician. If symptoms are severe take your child to the emergency department.

Although there is no evidence of an increased incidence of leukemia in patients treated with growth hormone and who do not have predisposing factors, some cases of leukemia have been reported in patients treated with somatropin for growth hormone deficiency. Inflammation of the pancreas has been described rarely.

Likewise, cases of sleep apnea and sudden death have been described in patients with Prader-Willi syndrome treated with growth hormone, as well as sudden appearance or accentuation of spine alignment disorders (scoliosis).

In cases where growth hormone deficiency is secondary to cancer treatments, there is a risk of reactivation and relapse of the tumor; this risk depends on the characteristics of the underlying disease or of the treatment used, as is the case with intracranial tumors and the previous requirement for radiotherapy. Patients with chronic overdosage can acquire acromegaloid features (excessive growth of certain parts of the body).

Finally, on rare occasions, the appearance of gynecomastia (development of breast tissue) has been described in prepubertal males treated with growth hormone.

If you consider that any of the adverse effects suffered by your child is serious or if you notice any adverse effect not mentioned in this document, you should inform the treating physician, as the dose may need to be reduced or the medication should be discontinued.

Are there long-term risks of using growth hormone?

The results of long-term follow-up studies of patients who have used growth hormone do not show a carcinogenic effect generated by the use of recombinant growth hormone in patients without previous cancer. The study of possible effects on bone cancer, bladder cancer and Hodgkin lymphoma is currently under investigation.

Is it possible to change the brand of the drug?

Somatropin is a biological medicine whose molecular structure is the same as that of the hormone naturally produced by the human body, so the risk of any adverse reaction is very low. When changing the brand of the drug, a response of the immune system (antibodies) that can affect the effectiveness of the drug in a low proportion is expected; however, the available evidence on possible effects on the results of treatment is scarce, so this consideration should be taken into account before starting the change to another brand of medicine and analyze the risks and benefits with the attending physician on an individual basis.

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What happens if I do not accept that my child receives the hormone?

Timely initiation of growth hormone treatment increases the likelihood of proper growth. Girls with Turner syndrome who do not receive treatment will express a much shorter stature than what is genetically expected, in addition to less accretion of bone mass. In general, if you decide not to start therapy, your child may have a delayed growth and short stature for age, which could have implications for his/her emotional and social health. Furthermore, up to now there are studies that suggest the possibility that this treatment reduces cardiovascular risk.

First and last name of the patient: _____
Type of document: _____ Document number: _____
Date of birth: _____
Age: _____ years _____ months _____

Through the legal representative (father or mother)
First name and last names: _____ Type of document: _____
Document number: _____
Indicate relationship (father, mother, legal guardian): _____

I declare that I have been informed by the physician
First name and last names: _____
Type of document: _____ Document number: _____
M.D. License: _____ Specialist in: _____

That, according to the diagnosis: _____, I have been told that my child should start drug treatment with growth hormone (somatropin), with the following characteristics:
Brand name: _____
Dosage (indicate route, dose, (mcg/kg/day) and frequency):_____
Expected duration of treatment: _____

Similarly, I have been informed about the effectiveness of the treatment:
An increase in final height is foreseeable in the accepted indications, ***but there is the possibility of non-response to treatment.*** There are no data available on final height in Turner syndrome for the Colombian population.

Description of personalized risks and probable discomforts (Information from the doctor regarding the particular circumstances of the patient _____
_____

Declaration of the patient and/or the caregiver:
After receiving this information, as the parent and/or his legal representative, **I declare that:**

- I have received the information from the doctor about the personalized risks of the treatment and have read the package leaflet of the pharmaceutical specialty.

- I am satisfied with the information received and have obtained clarification from the doctor about the doubts raised.

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- I know the possibility of revoking the consent given at any time, without expression of cause and without consequences for future care.

- I accept to be included and attend the medical appointments of the growth hormone program within the established for the control and follow-up of the patients with use of it as a requirement to continue the provision of the supplies and the drug.

Data collection:
I _____identified with _____ number _____ from _____ authorize the medical staff of the institution **to prescribe GROWTH HORMONE (SOMATROPIN) to my child.**

Likewise, I declare, having the legal capacity to do so, that:
• I have been informed about the nature and purpose of the procedures described in this document, as well as on what is related to the most frequent complications derived from them; furthermore, I have been given the opportunity to ask questions and all of them have been answered to my satisfaction.
• I have been informed of the alternative treatment methods, in case there was any, as well as of the advantages and disadvantages of each of them.
• I informed the doctor of the current condition and general diseases of my child for the assessment of possible contraindications.
• I am aware that I can withdraw or revoke the authorization for the use of the medicine if I deem it appropriate, without this having an impact on medical care.
• I am aware of the risks of the indicated treatment.
• I have been informed that there are no absolute guarantees that the result of the treatment will be satisfactory.

I, Dr. _____, as treating physician, after explaining to the legal representative of the patient the procedure and the content of this document, I have asked him/her if he/she wants additional information or if he/she has any concerns about the treatment, to which he/she stated_____
_____
In the same way, the legal representative of the patient is consulted if he authorizes taking photographs and recording the intervention for academic or scientific purposes without his name or that of his relatives being disclosed, to which he replied: YES____ NO____
In witness thereof, it is signed in _____, on the _____ day of the month of _____ 20_____
Name of the legal representative of the patient: _____
ID card: _____
Signature: _____**Fingerprint:**
Physician (Signature and Stamp):_____
M.D. License: _____**Fingerprint:**

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Annex 4. Informed dissent for the initiation of treatment with somatropin

INFORMED DISSENT

I _____identified with _____ number _____ from _____, after being informed of the nature and risks of the administration of growth hormone (somatropin), the consequences of non-application and the absence of alternatives for the treatment of my illness or that of my child, in the light of current scientific knowledge present, I freely and consciously manifest the DENIAL OF CONSENT for its realization, making myself responsible for the consequences that may arise from this decision, for the following reason(s):_____ _____

In witness thereof, it is signed in _____, on the _____ day of the month of _____ 20_____

Name of the legal representative of the patient: _____
ID card: _____

Signature: _____Fingerprint:
Physician (Signature and Stamp):_____
M.D. License: _____ Fingerprint: