Prospecto
INGLÉS

BIOSIDUS

Producto: HHT® (Somatropina) - Inyectable liofilizado		
Tamaño: 330 x 240 mm Material: Papel Obra Primera alisado Gramaje: 50 g/m² (47,5 - 52,5) g/m² Tamaño final doblado: 165 x 40 mm (tolerancia máx. 2 mm)	**Código: 153953** **Fecha: 12/2021** Reemplaza a: 153235	Cambios: Cambio de DT a Paula Olcese

Realizado por:	Aprobado por:	Aprobado por:	Aprobado por:	Aprobado por:	Aprobado por:	Aprobado por:
Desarrollo de PKG (Firma y Fecha)	Investigación Clínica (Firma y Fecha)	Control de Calidad (Firma y Fecha)	Comercial (Firma y Fecha)	Producción / QA (Firma y Fecha)	Asuntos Regulatorios (Firma y Fecha)	Dirección Técnica (Firma y Fecha)

PANTONE 425 U

330 x 240 mm PANTONE 425 U

SENTIDO DE LECTURA PHARMACODE

BIOSIDUS

HHT®

SOMATROPIN 4 I.U. (1.33 mg)/16 I.U. (5.32 mg)

Lyophilized for injection (S.C. - I.M.)

Made in Argentina – Prescription drug

PROPERTIES:
Somatropin or the growth hormone (GH) is one of the most abundant hormones produced by the anterior pituitary lobe. It is synthesised and secreted by specific cells, the somatotropes. GH daily secretion varies through life: its concentration is high in children, reaching maximum levels in adolescence, while in adulthood, the concentration decreases progressively. GH secretion occurs in a pulsatil and irregular way; between pulses, the flowing GH decreases up to levels that are sometimes non-detectable through some of the current methodologies. Secretion pulse amplitude achieves maximum levels at night and the most constant GH secretion occurs little after deep sleep onset.

HHT® contains somatropin, the recombinant human growth hormone, whose amino acid sequence is identical to the natural human growth hormone. Somatropin, HHT® active ingredient, is made up of a unique 191-amino-acid polypeptide chain. Its molecular weight is 22,124 Da; it contains two disulphide bonds and it is not glycosylated. It is produced by recombinant DNA technology in E. coli bacteria cultures. Subsequent purification stages guarantee the production of a highly purified human growth hormone, suitable to be used as the active pharmaceutical ingredient of HHT®.

COMPOSITION:

Each vial with lyophilized HHT® 4 IU contains:

Somatropin	4 IU (1.33 mg)
Glycine	24.00 mg
Anhydrous sodium dibasic phosphate *	0.26 mg
Anhydrous sodium monobasic phosphate *	0.26 mg

*Or its equivalent in the same salts with a set degree of hydration

Each prefilled syringe with diluent contains:

Distilled water for injection	1.0 mL

Each vial with lyophilized HHT® 16 IU contains:

Somatropin	16 IU (5.32 mg)
Glycine	2.00 mg
Mannitol	41.00 mg
Anhydrous sodium dibasic phosphate *	0.26 mg
Anhydrous sodium monobasic phosphate *	0.26 mg

*Or its equivalent in the same salts with a set degree of hydration

Each ampoule with diluent contains:

Distilled water for injection	1.0 mL
m-Cresol	3.0 mg

CLINICAL PHARMACOLOGY
In pre-clinical and clinical trials, Somatropin has demonstrated to be therapeutically equivalent to the naturally occurring growth hormone in the pituitary gland. In pediatric patients who show growth hormone deficiency (GHD) or Turner syndrome or Prader-Willi syndrome (PWS), or those who were born small for their gestational age and did not show improvement regarding height by two y.o. or older, Somatropin treatment stimulates lineal growth. In Somatropin-treated GHD patients, Insulin-like Growth Factor I (IGF-I) levels achieve normal status. In GHD adults, Somatropin treatment reduces the adipose tissue, increases the muscular mass, produces metabolic alterations including beneficial changes on the lipid metabolism and takes IGF-I concentrations to normal levels.

Somatropin stimulates the human growth and it also has other functions:
- Regarding the glucidic metabolism, it reduces the tolerance to carbohydrates. Pediatric patients, mainly throughout neonatal period with hypopituitarism and GHD, may experience hypoglycemia when fasting, which can be reverted by HHT® treatment. Large HHT® doses or its use in healthy volunteers may alter the tolerance to glucose.
- Regarding the adipose metabolism, it has lipolytic effect. In GHD patients, somatropin administration causes lipid mobilisation, while reducing the body fat and increasing free fatty acids levels in plasma.
- Regarding the protein metabolism, it shows anabolic effect. The lineal growth is partly facilitated through the increase of the protein synthesis at cellular level. At somatropin-therapy onset, nitrogen retention plus decrease of nitrogen excretion at urinary level occur.
- Regarding electrolytic metabolism, somatropin causes the retention of sodium, potassium, water and phosphorus. The serum concentration of inorganic phosphate is increased in GHD patients post somatropin treatment. The calcium level in serum does not show meaningful distortions by somatropin treatment, probably causing a transitory increase at treatment onset (throughout the first 6 months), reflecting an increase over the bone turnover as a consequence of growth. The growth hormone may transitorily increase the calciuria (around the third month of treatment) with later decrease.
- Regarding bone growth, somatropin triggers such growth in pediatric patients with GHD, Turner syndrome, intrauterine growth retardation with no ponderal gain and PWS. Body length growth is the result of somatropin effect over the epiphysiary plates of long bones. IGF-I concentrations, which play a very important role in bone development, are low in GHD pediatric patients, but they increase under somatropin treatment, as well as alkaline phosphatase serum level (bone growth marker).
- At body composition level, somatropin-treated GHD adult patients, at recommended doses, showed a decrease over the body adipose mass and an increase over the lean mass.

MECHANISM OF ACTION
Somatropin, as well as the endogenous GH, functions by means of binding to specific receptors on the surface of numerous cells. The activation of these receptors triggers a cascade of intracelular events, particularly phosphorilations, which conclude on the regulation of the expression of several genes, at transcription level. The majority of somatropin anabolic effects are mediated by IGF-I, synthesised in the liver, and other tissues in response to the stimulation of GH receptors on its membrane. IGF-I concentrations are low in GHD pediatric patients, but they get to normal levels after somatropin treatment.

PHARMACOKINETIC PROPERTIES
Absorption: 80% of somatropin is absorbed when it is injected subcutaneously. Using HHT®, maximum plasma concentration is reached approximately 3.27 ± 1.08 hours following SC administration in healthy volunteers, showing an absorption half-life of around 0.75 hours. Following HHT® administration at 4 IU, plasma peak (as geometric average and 95% confidence interval) in healthy adult volunteers was 8.32 ± 3.42.

Distribution: The apparent average distribution volume for somatropin following its administration, 4 IU, to healthy volunteers is 139.10 ± 69.40 l/kg; in GHD adults it has been estimated at 1.3 ± 0.8 l/kg. It mainly reaches highly perfunded organs.

Excretion: Somatropin is mainly excreted by renal and hepatic proteolysis. Approximately 0.1% of the dose is excreted unaltered. In a study involving healthy volunteers following the administration of 4 IU, the elimination half-life HL Lambda was 4.22 ± 1.59 hours. HHT® serum concentrations decrease following SC injection to healthy volunteers showing half-life: 6 hours, approximately.

Duration of action: Between 12 and 48 hours, approximately.

Specific populations and genre: No studies have been performed assessing HHT® pharmacokinetics in pediatric patients. As regards GHD in adults, it has been reported that somatropin bioavailability was similar in men and women.

THERAPEUTIC INDICATIONS:
HHT® is indicated for:
1. Long term treatment in pediatric patients showing growth retardation confirmed by inadequate secretion of the growth hormone.
2. Long term treatment in pediatric patients showing growth retardation confirmed by renal insufficiency.
3. Long term treatment in PWS pediatric patients. PWS diagnosis should be confirmed by an appropriate genetic test.
4. Long term treatment in TS pediatric patients. It should be confirmed by an appropriate genetic test.
5. Long term treatment in pediatric patients who were born smaller regarding their gestational age and who show growth retardation and lack of height recovery at two years of age.
6. GHD replacement treatment in adults regarding the presence of the following criteria:
a) GH Deficiency in adults, isolated or with multiple hormone deficiency that developed as the result of a hypothalamic or pituitary illness, irradiation or surgery. GH Deficiency initiated in childhood, which was not confirmed till adulthood.
b) When the result of the GH stimulation standard test is negative, reaching a maximum peak below 5 ng/mL through radioimmunoassay (RIA) or below 2.5 ng/ml when it is assessed using monoclonal antibodies (IRMA).
7. Wasting syndrome in AIDS (Acquired Immunodeficiency Syndrome) patients: This syndrome, frequent in AIDS patients, implies a decline in the quality of life and, in extreme cases, it jeopardises the patient's life. In AIDS patients, loss of weight and muscular mass is associated with a major incidence of traumatisms caused by accidents. HHT® can be used in patients infected with the Human Immunodeficiency Virus (HIV) when its administration is monitored by an experienced physician regarding diagnosis and treatment of AIDS patients.
Before HHT® treatment onset, it is important to discard other causes that might cause cachexia and weight loss in AIDS, including insufficient nutritional supply, a secondary infection (for example, tuberculosis), incapacity to maintain an appropriate food intake (for example, oral or esophageal complications), malabsorption syndrome, lethargy, neoplasia, depression, suprarenal insufficiency or hypogonadism.

POSOLOGY:
The dose should be determined individually. The following recommendations are based on the applied dose in controlled clinical trials that demonstrated the efficacy of the treatment.
- *Growth hormone deficiency in pediatric patients:* Doses between 0.5 and 0.7 IU/Kg of weight per week are recommended or 12 IU/m2 per week, divided into 6 or 7 SC, or 2 or 3 IM injections. It is suggested to change the site of injection in order to avoid lipoatrophy.
- *Turner Syndrome in pediatric patients:* The recommended dose is 0.7 to 1 IU/Kg of weight/week SC, divided into 6 or 7 SC, or 2 or 3 IM injections. It is suggested to change the site of injection in order to avoid lipoatrophy.
- *Prader-Willi Syndrome in pediatric patients:* The recommended dose is 0.72 to 1 IU/Kg of weight per week SC, divided into 6 or 7 SC, or 2 or 3 IM injections. It is suggested to change the site of injection in order to avoid lipoatrophy.
- *Small pediatric patients regarding their gestational age*: The recommended dose is 1 to 1.44 IU/Kg of weight per week SC.
- *Growth Hormone Deficiency in adult patients:* It is recommendable to start on 0.12 IU/kg of weight per week. The dose can be increased regarding a 4 to 8 week-interval, depending on the patient's individual requirements, till a maximum of 0.24 IU/Kg of weight per week, divided into 6 or 7 SC, or 2 or 3 IM injections. It is suggested to change the site of injection in order to avoid lipoatrophy.
- *Chronic renal insufficiency in pediatric patients:* SC injection at 45-50 µg/kg per day (0.135 – 0.15 IU/kg per day) or 1.4 mg/m2 per day (4.2 IU/ m2 per day).
The dose can be adjusted based on medical criteria, regarding IGF-I levels.
- *Wasting Syndrome in AIDS patients:* It is defined as the non-intentional weight loss, equal or over 10% of basal body weight (the habitual for the patient), associated with chronic diarrhoea or fever, with no concomitant cause (it is necessary to discard those mentioned above). The applied dose in trials involving somatropin varies from 0.26 to 0.3 IU (0.1 mg)/kg of weight/day. There is no consensus regarding the duration of the treatment. Since available trials are based on 12-week therapies, efficacy in longer periods of treatment has not been assessed. After treatment onset, adverse reactions should be thoroughly evaluated and treated symptomatically; if the adverse reaction is severe, HHT® dose should be reduced or withdrawn. In the mentioned trials, the response was assessed two weeks post treatment onset. If the patient stops losing weight, HHT® administration should be resumed. On the contrary, if the patient continues losing weight, a new research should be done regarding the eventual presence of a concomitant clinical cause, such as an opportunist infection. If this condition is detected, appropriate treatment should be applied together with the administration of HHT®. After 6-treatment weeks, the muscular mass should be assessed: if it remains the same or increases, the treatment should be continued till completing twelve weeks; if it decreases, HHT® treatment should be withdrawn, deepening the search for a concomitant clinical cause.

RECONSTITUTION:
Reconstitute the content of an ampoule of HHT® with one millilitre of water for injection from the ampoule with the solvent, making it flow against the vial wall. After reconstitution, swirl the vial with gentle rotary motion until the content is completely dissolved.
Do not shake the solution during preparation.
Before administration, the stopper should be cleaned with a swab embedded in isopropyl alcohol in order to avoid contamination.

CONTRAINDICATIONS:
HHT® should not be administrated when there is evidence of active neoplasia. If there are neoplasia antecedents, HHT® treatment should be initiated once the corresponding anti-neoplastic treatment is over. If there is evidence of active tumor, HHT® treatment should be withdrawn. HHT® should not be administered to stimulate growth in children with closed epiphysis.

It is recommendable not to initiate HHT® treatment either in patients suffering complications from open-cast method, abdominal surgery or traumatism, or in those who show acute respiratory failure. The growth hormone is contraindicated in severely obese PWS patients or in those who show an important respiratory deterioration as confirmed by spirometry.

PRECAUTIONS:
HHT® treatment should be indicated by a specialist physician who, based on appropriate tests, should verify the diagnosed growth hormone deficiency before treatment onset, as well as the eventual presence of distortions regarding other adenopituitary hormones.

Under HHT® therapy, a thorough control should be performed in patients with diabetes, glucose intolerance or risk factors such as obesity or family history of diabetes, Type II. In insulin-dependent patients, the insulin dose should be periodically adjusted.

Some leukaemia cases have been detected in somatropin-treated children, registering a slightly higher frequency than that observed in children without the growth hormone deficiency, but no cause relationship could be established.

Some patients may develop hypothyroidism under HHT® treatment; thus patients should undergo regular controls regarding thyroid function.

Pediatric patients with endocrine disorders, including GHD, show a high incidence of luxation on femoral epiphysis. Under HHT® treatment, presence of limp or pain development on hips or knees should be careful evaluated.

Patients with GHD secondary to an intracranial lesion should be frequently examined regarding recurrence or progression of the disease.

Development of skin lesions, suspicious of malignancy, should be monitored.

Scoliosis may progress in those who experience a fast growth. Consequently, HHT® - treated patients with history of scoliosis should be monitored for illness progression risk. However, it could not be demonstrated that somatropin treatment increases scoliosis incidence. Scoliosis is common in non-treated PWS patients; physicians should assess the possible presence of this abnormality which might become evident under somatropin treatment.

Cases of intracranial hypertension with papilloedema, visual changes, headaches, nausea and/or emesis have been registered in a small number of growth hormone-treated patients. Generally, symptoms occur within the first 8-treatment weeks. In all reported cases, these symptoms disappeared once the therapy was over or after dose reduction. It is recommendable to perform a fundus oculi exam at treatment onset and periodically during treatment. PWS patients and chronic renal insufficiency have a higher risk of developing endocranial hypertension.

There are no studies demonstrating if somatropin alters the reproductive capacity or if it is harmless during pregnancy and lactation.

WARNINGS:
The human growth hormone is classified as a controlled and forbidden substance in the practice of sports (Class E, Peptide Hormones: Mimetic and analogue). Sportsmen should be warned about HHT® active ingredient, since it may cause a positive result in antidoping tests.

ADVERSE EFFECTS:
Adverse effects have been reported in less than 1% of the patients treated with the human recombinant growth hormone, mainly as transient reactions over the injection site.
The long-term use of the human growth hormone at excessive doses in patients who are not deficient in it, might originate acromegalic features on the face, hands, feet and other related clinical signs, including visceromegaly, diabetes, atherosclerosis, arterial hypertension and carpal tunnel syndrome.
The development of antibodies against the growth hormone may occur in a small number of patients. Interference with treatment response regarding growth has been described if and only if the binding capacity is above 2 mg/l.
As frequent adverse effects, otitis media or hearing conditions in patients with Turner syndrome have been registered. During somatropin treatment, carpal tunnel syndrome, gynecomastia, headache, mole growth increase, articular and muscular pain, peripheral edema, general weakness, rash, jaundice, intracranial hypertension (blurred vision, headache, nausea, emesis, papilledema) and lipodystrophy on the injection site, which may be reduced by rotating it, have been described.
Intracranial hypertension symptoms usually occur within the first 8 treatment weeks and they disappear through dose reduction or through therapy interruption.

Vulnerable Population
Children
Infrequent reactions over the injection site (with pain, swelling, burn sensation, fibrosis, nodules, rash, pigmentation, lipoatrophy, bleeding) hematuria, hypothyroidism, mild hyperglycemia, pancreatitis (abdominal pain, distension, nausea, emesis) and subluxation of the femoral head (limp, hip or knee pain) have been registered.

AIDS Patients
In controlled trials, treatment interruption due to adverse events fell below 10% and similarly among those patients who were receiving growth hormone and those who were receiving placebo. Adverse events caused or not by growth hormone were:
1) Infections (especially *Pneumocystis carinii*). 2) Kaposi's Sarcoma. 3) Edema.
4) Neurological conditions: paresthesias, headaches, convulsions, hypertonia, nystagmus, meningeal symptoms, tremor. 5) Breathing disorders: dyspnoea, cough, sinusitis, infections of the upper respiratory tract, pharyngitis, rhinitis, pneumonia, bronchitis, pleurisy. 6) Gastrointestinal distortions: abdominal pain, gingivitis, gastritis, diarrhea, dyspepsia, pancreatitis, hepatitis, alitiasic cholestasis. 7) Hematologic distortions: lymphoadenopathy, eosinophily, trombocitopenia. 8) Carpal tunnel syndrome. 9) Skin distortions: rash, pruritus, hyperpigmentation, folliculitis, acne, alopecia, pain on the injection site, ulcers on the skin. 10) Psychiatric disorders: depression, anxiety, somnolence, thought distortions. 11) Ocular distortions: retinitis, photophobia. 12) Hepatic function distortions. 13) Gynecomastia and pain in the mammary gland 14) Auditory distortions. 15) Cardiovascular distortions: precordial pain, hypertension and hypotension, ECG abnormalities, cardiac murmur. 16) Alterations on lab tests: increase of triglicerids, increase of alkaline phosphatase, increase of CPK and LDH, glycosuria, hypokalemia, acidosis, hypoalbuminemia. 17) Epididymitis and penis alterations. 18) Others: arthralgia, fatigue, muscular weakness, mucous dryness, oral leukoplasia.
The edema, the arthralgias or mialgias and the diarrhea were more frequent in the treated patients than in those who were not treated. Development of specific antibodies was not observed.
Dose modification due to adverse reactions in somatropin-treated AIDS patients: The dose should be reduced 50% when the following is observed: 1) Triglicerids over 7.9 mmol/l and glycemia over 8.9 mmol/l; 2) Mild arterial hypertension; 3) Non-responding arthralgias to anti-inflammatory administration; 4) Carpal tunnel syndrome; 5) Non-responding edema to diuretic administration; or 6) Severe paresthesias. Treatment should be withdrawn if: 1) triglicerids over 16.9 mmol/l and glycemia over 8.9 mmol/l; 2) Brain pseudo-tumor; 3) Congestive cardiac insufficiency; 4) Pancreatitis; 5) Hypertension over 200/100 mm Hg; 6) Severe allergy; or 7) Untreatable paresthesias.
Safety and efficacy of somatropin treatment in AIDS pediatric patients have not been completely assessed yet.

ANTAGONISMS AND ANTIDOTES:
Resistance to the growth hormone action may be observed in patients with hypercatabolic signs, such us the wasting syndrome associated to HIV infection, and in patients with anti-growth hormone antibodies. Specific antidotes used today against somatropin are still unknown.

Interactions with other medicinal products:
The concomitant administration of glucocorticoids may inhibit HHT® effect over growth (apart from reducing the endogenous production of the growth hormone). In case of associated ACTH production deficit, the treatment should be adjusted by means of glucocorticoids in order to minimise the inhibitory effect over growth.

In diabetic patients, the growth hormone administration may cause resistance to insulin. Therefore, it is advisable to regularly control glucose levels.

There is preliminary evidence of regulation of several cytochrome P 450 isoforms by the growth hormone. Potentially speaking, the growth hormone may alter the metabolism of some drugs which are metabolised by the cytochrome P 450 system. It is therefore advisable to perform a thorough control when HHT® is concomitantly administrated with cytochromes P 450-metabolised drugs.

Carcinogenesis - Mutagenesis
No trials on carcinogenesis have been carried out either in animals or in human beings. Preliminary trials performed with somatropin in animals and in cell cultures did not reveal any mutagenic potential, although this should still be confirmed.

Pregnancy - Fertility
No trials have been performed in human beings. Trials developed in rats and rabbits, using doses 31 and 62 times above the pediatric dose (based on body surface), did not show that somatropin causes adverse effects in the fetus or impairment in fertility. Somatropin belongs to the B category within the FDA classification (trials performed in animals did not show evidential risk, but there is no data in humans).

Lactation
There is no certainty whether the growth hormone is secreted through maternal milk during lactation.

Elderly people
No clinical trial has assessed the safety and efficacy of the growth hormone in adults over 65 years old or more. Elderly patients may be more sensitive to the action of somatropin and more susceptible to develop adverse events.

OVERDOSE
No data of HHT® overdose is available; however, some isolated cases have been reported after using some other somatropin preparations.

<u>The clinical effects caused by overdose in such cases included:</u>
Acute: Initial hypoglycemia, followed by hyperglycemia.
Chronic: similar signs or symptoms described for acromegaly (amenorrhea, back ache, vision changes, excessive sweating, extreme weakness, increase of head size, hands and feet, articular and limb pain, polyuria, polydipsia).
In case of an overdose, attend to the nearest hospital or phone Toxicology Centres.

STORAGE:
HHT® 4 IU should be stored in the refrigerator (between 2 °C and 8 °C), protected from light.
After reconstitution, HHT® 4 IU can be used within the 7 subsequent days, keeping it refrigerated between 2 °C and 8 °C.
HHT® 16 IU should be stored in the refrigerator (between 2 °C and 8 °C), protected from light.
After reconstitution, HHT® 16 IU can be used within the 3 subsequent following weeks, maintaining it refrigerated between 2 °C and 8 °C.

IN CASE OF FREEZING, DISCARD THE PRODUCT
THIS MEDICATION IS ONLY AVAILABLE ON PRESCRIPTION
ITS ADMINISTRATION SHOULD BE MONITORED BY THE PHYSICIAN
KEEP OUT OF REACH OF CHILDREN

Medicinal speciality authorised by the Ministry of Health. Certificate N° 46.109

Manufactured by:
BIOSIDUS S.A.
Constitución 4234 (C1254ABX) Buenos Aires, Argentina.
Technical Director: Pharm. Paula Olcese.

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