BIOSIDUS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

HHT® 16 I.U./1 mL lyophilized powder for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one vial contains 16 I.U. (5.32 milligrams) of somatropin produced in *Escherichia coli* cells by recombinant DNA technology, in 1 mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Vials contain white lyophilized powder.

Diluent is clear and colorless.

4. CLINICAL DATA

4.1. Therapeutical indications

HHT® is indicated for:

1. Long term treatment of pediatric patients with growth retardation due to the inadequate secretion or deficiency of growth hormone.

2. Long term treatment of pediatric patients with growth retardation secondary to renal failure.

3. Long term treatment of PWS pediatric patients. PWS diagnosis must be confirmed by an appropriate genetic test.

4. Long term treatment of pediatric patients with Turner syndrome. It should be confirmed by an appropriate genetic test.

5. Long term treatment of pediatric patients born small for their gestational age with growth retardation and lack of height catch up at the age of two.

6. Treatment of idiopathic short stature (ISS), also called short stature with no growth hormone deficiency and defined as the score of the stature standard deviation (SDS) ≤-2.25 and associated to growth rates which do not allow for achieving a normal range of adult stature, in pediatric patients with open epiphysis GHD whose diagnostic assessment excludes other causes of short stature which could be treated otherwise.

7. GH replacement treatment in GHD adults if any of the following criteria apply: a) GH deficiency in adults, isolated or with multiple hormone deficiency developed as the result of a hypothalamic or pituitary illness, irradiation, surgery or trauma. GH deficiency of childhood onset which was not confirmed till adulthood. b) Patients with human growth deficiency treated with somatropin in childhood whose epiphysis are closed should be re-assessed before somatropin therapy continuation at the level of reduced dose recommended with adults with growth hormone deficiency. According to current treatment standards, the confirmation of growth hormone deficiency in adults in both groups implies a GH stimulation standard test with two exceptions: 1) patients with deficiency of other pituitary hormones caused by an organic disease; and (2) patients with congenital / genetic growth hormone deficiency.

8. Wasting syndrome in AIDS (Acquired Immunodeficiency Syndrome) patients: This syndrome, frequent in AIDS patients, implies a decline in the quality of life and, might eventually jeopardize 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 in the diagnosis and treatment of AIDS patients. Before initiating HHT® treatment, other causes of cachexia and weight loss should be discarded, including insufficient nutritional intake, a side infection (i.e., tuberculosis), inability to maintain an appropriate food intake (for example, oral or esophageal complications), malabsorption syndrome, lethargy, neoplasms, depression, suprarenal insufficiency or hypogonadism.

4.2. Posology and method of administration

Dosage

Dosage should be determined on a case-by-case basis. The following recommendations are indicative of the dosage schemes used in controlled clinical trials that demonstrated the efficacy of somatropin treatment.

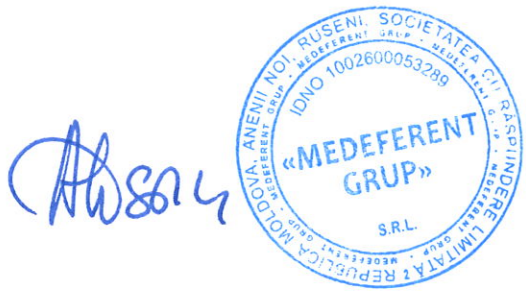
Growth hormone deficiency in pediatric patients: Subcutaneous or intramuscular injections at doses of 23-29 micrograms/kg/day (0.5 to 0.7 IU/Kg or 0.25 to 0.30 mg/kg body weight weekly) or 0.7–1 mg/m^2/day are recommended. It is recommended to split the doses into 6 or 7 subcutaneous injections or 2 to 3 intramuscular injections weekly. It is also recommended to change the site of injection in order to avoid lipoatrophy.

Turner Syndrome in pediatric patients: Subcutaneous injection of 45–50 micrograms/kg/day (0,7 to 1 IU/kg or 0.25 to 0.33 mg/kg body weight/weekly) or 1.4 mg/m^2/day. It is recommended to split the doses into 6 or 7 subcutaneous injections or 2 to 3 intramuscular injections weekly. It is also recommended to change the site of injection in order to avoid lipoatrophy.

Prader-Willi Syndrome in pediatric patients: Subcutaneous injection in children with growth velocity above 1 cm/year in combination with a hypocaloric diet, 35 micrograms/kg/day (0.7 to 1 IU/kg or 0.25-0.33 mg/kg body weight weekly) or 1 mg/m^2/day; maximum 2.7 mg/day. It is recommended to split the doses into 6 or 7 subcutaneous injections or 2 to 3 intramuscular injections weekly. It is also recommended to change the site of injection in order to avoid lipoatrophy.

Small for gestational age patients: Subcutaneous injection, 35 micrograms/kg/day (0.7 to 1 IU/Kg to 0.25-0.33 mg/kg body weight weekly) or 1 mg/m2/day.

Growth Hormone Deficiency in adult patients: Subcutaneous injection initially at 150-300 micrograms daily (0.12 IU/kg or 0.05 mg/kg body weight weekly) and if required, gradually increased till a maximum of 1 mg/day; apply the minimal effective dose (requirements may diminish with age). It is recommended to split the dosage into 6 or 7 subcutaneous injections or 2 to 3 intramuscular injections weekly. It is also recommended to change the site of injection in order to avoid lipoatrophy.



Chronic renal failure in pediatric patients (less than 50 % impaired renal function): Subcutaneous injection at 45-50 µg/kg/day (0.7 to 1 IU/kg/week or 0.25-0.33 mg/kg/week) or 1.4 mg/m^2/day (higher doses may be required) and adjusted -if required, after 6 months. Dose can be adjusted based on medical criterion, assessing IGF-I levels.

Wasting Syndrome in AIDS patients: Defined as the involuntary loss of weight equal to or more than 10% of basal body weight (the habitual for the patient), associated with chronic diarrhea or fever, with no concomitant cause (it is necessary to discard those mentioned above). By subcutaneous route, 100 micrograms/kg/day (0.26 to 0.3 IU or 0.1 mg/kg body weight/day up to a maximum of 6 mg for 48 weeks. There is no consensus regarding treatment duration. Since available trials are based on 12-week treatments, 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 discontinued. In the abovementioned trials, response was assessed two weeks post treatment onset. If patients cease losing weight, HHT® administration should be continued. On the contrary, if patients keep on losing weight, the eventual occurrence of a concomitant clinical cause, such as an opportunist infection should be assessed. If so, appropriate treatment should be applied together with the administration of HHT®. After 6 weeks of treatment muscle mass should be evaluated: if it remains the same or increases, treatment should be continued till completing twelve weeks; if it decreases, HHT® treatment should be suspended, deepening the search for a concomitant clinical cause.

Idiopathic short stature (ISS) in pediatric patients: by subcutaneous route, up to 0.053 mg/kg body weight/day (up to 0.3 – 0.37 mg/kg body weight/week). However, due to the variability in response of these patients, an individualized dose adjustment may be necessary to optimize growth and prevent side effects.

Special populations

Elderly

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.

Dose modification due to adverse reactions in somatropin-treated AIDS patients:

-The dose should be reduced by 50% when the following is observed: 1) Triglycerides 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) Edema irresponsive of diuretic administration; or 6) Severe paresthesia.

- Treatment should be discontinued if: 1) triglycerides 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 paresthesia.

Safety and efficacy of somatropin treatment in AIDS pediatric patients have not been completely assessed yet.

Method of administration

HHT® is administered by subcutaneous route. In order to prevent local lipoatrophy and reactions in the injection site, it is recommended that patients rotate sites of injection each time they apply HHT®.

For instructions for use and handling see section 6.6.

4.3. Contraindications

HHT® should not be administrated when there is evidence of active neoplasms. In case of history of neoplasms, HHT® treatment should be initiated once the anti-neoplastic treatment has been concluded. If there is evidence of active tumor, HHT® treatment should be discontinued. Since growth hormone deficiency may be an early sign of pituitary tumor (or, rarely of other brain tumors), the occurrence of said tumors should be discarded before starting treatment. Somatropin should not be used in patients with evidence of progression or recurrence of an underlying intracranial tumor.

HHT® should not be administered to stimulate growth in children with closed epiphysis.

Patients with acute critical illness. It has been reported an increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or trauma, or patients with acute respiratory failure. It is recommended not to initiate HHT® treatment on these patients.

Growth hormone is contraindicated in severely obese PWS patients or in those who show a severe respiratory impairment assessed by spirometry.

HHT® is contraindicated in patients with known hypersensitivity of somatropin or any of its excipients (See section 6.1).

Somatropin is contraindicated in patients with active proliferative diabetic retinopathy or severe non proliferative diabetic retinopathy.

Somatropin should not be used after kidney graft.

Somatropin should not be administered in patients with chronic liver impairment.

Pregnancy (See section 4.6)

Breast feeding (See section 4.6.)

4.4. Special warnings and precautions for use

HHT® treatment should be indicated by a specialist physician who, based on appropriate tests, should validate the growth hormone deficiency diagnosis before treatment onset, as well as the eventual presence of disorders of other adenopituitary hormones.

The maximum recommended daily dose should not be exceeded (see section 4.2).

Impaired Glucose Tolerance and Diabetes Mellitus

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 type II diabetes. In insulin-dependent patients, the insulin dose should be periodically adjusted.

Malignancies

In patients who suffered cancer in childhood and who were treated with brain/head radiotherapy for their former neoplasms, and who developed subsequent GHD and were treated with somatropin, an increase in the risk of a second neoplasms have been reported. Intracranial tumors -particularly meningiomas, were the most commonly reported second neoplasms. In adults, it is unknown if there is any relationship between somatropin replacement therapy and CNS tumor recurrence. All patients with history of GHD secondary

to intracranial neoplasms should be routinely monitored during somatropin treatment to assess tumor progression or recurrence.

Since children with some rare genetic causes of short stature have a higher risk of developing malignant tumors, it is necessary to weigh risks and benefits of starting somatropin treatment. In case these patients start treatment with somatropin, they should be carefully monitored for development of neoplasms. Patients on somatropin should be closely monitored to detect a higher growth or possible malignant changes of preexisting tumors.

Patients with secondary GHD to an intracranial lesion should be frequently monitored for disease recurrence or progression.

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

Leukemia

Some leukemia cases have been reported in children on somatropin treatment at a slightly higher frequency than that observed in children with no growth hormone deficiency. However, no causal relationship could be established.

Severe hypersensitivity

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products.

Patients and caregivers should be informed that such reactions are possible, and that prompt medical attention should be sought if an allergic reaction occurs.

Thyroid function

Some patients on somatropin treatment may develop hypothyroidism; therefore, HHT® treated patients should be regularly monitored for thyroid function.

Slipped capital femoral epiphysis

Pediatric patients with endocrine disorders, including GHD, show an increased incidence of luxation on femoral epiphysis. During HHT® treatment, the onset of a limp or pain in hips or knees should be carefully evaluated.

Progression of preexisting scoliosis

Scoliosis may progress in those who experience a rapid growth. Consequently, HHT®-treated patients with history of scoliosis should be monitored for the risk of illness progression. However, there lacks evidence to demonstrate that somatropin treatment increases scoliosis incidence. Scoliosis is common in non-treated Turner syndrome or PWS patients; physicians should assess the possible presence of this abnormality which might become evident under somatropin treatment.

Intracranial hypertension

Cases of intracranial hypertension with papilledema, visual changes, headaches, nausea and/or emesis have been registered in a small number of growth hormone-treated patients. Generally, symptoms occur within the 8 first weeks of treatment. In all reported cases, these symptoms disappeared once the therapy was concluded or following dose reduction. It is advisable to perform a fundus oculi exam at treatment onset to discard pre-existing papilledema and periodically thereafter during treatment. Should papilledema occur, treatment should be discontinued. In case somatropin induced intracranial pressure is diagnoses, HHT® treatment may be resumed at lower doses once high intracranial pressure signs and symptoms have disappeared. Turner syndrome patients may be at higher risk of occurrence of intracranial pressure increase. Patients with PWS and chronic renal failure are at a higher risk of developing endocranial hypertension.

Patients with Prader-Willi syndrome

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at higher risk than females. Patients with PWS should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or sleep apnea, treatment should be interrupted. All patients with PWS treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and properly treated.

Fluid retention

In adult patients, fluid retention during somatropin therapy may occur. Clinical manifestations of fluid retention (i.e., edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome and paresthesias) are usually transient and dose dependent.

Hypoadrenalism

Patients on somatropin therapy who have or are at risk for pituitary hormone deficiency may be at risk or reducing serum cortisol levels and/or unmasking secondary hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require a dose increase following initiation of somatropin treatment.

Patients with Turner Syndrome

Turner syndrome patients should be carefully evaluated for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (i.e., stroke, aneurysm, aortic dissection, hypertension) since these patients are also at risk for these conditions.

Local reactions

When somatropin is administered by subcutaneous route at the same site for a long time span, lipoatrophy may occur. This can be prevented by rotating the site of injection.

Laboratory tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-I may increase during somatropin therapy.

Pancreatitis

Cases of pancreatitis have been rarely reported in children and adults on somatropin treatment. Some evidences suggest a greater risk in children as compared to adults. Published literature indicates that girls with Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin–treated patient, especially a child, who develops persistent intense abdominal pain.

Pregnancy and breast feeding

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

Children small for gestational age

It is recommended not to initiate somatropin treatment close to puberty in children born small for their gestational age. Experience in patients with Silver-Russell syndrome is limited.

Somatropin abuse

Human growth hormone is classified as a controlled and forbidden substance in the practice of sports (Class E, Peptide Hormones: Mimetic and analogues). Sportsmen should be warned about HHT® active ingredient, since it may render a positive result in antidoping tests. For current updated information, check the list of prohibited substances published by the Nation's Secretariat of Sports.

Metacresol

HHT® contains metacresol as an excipient. Metacresol in concentrations greater than 3.5 mg has been associated with local irritation and tissue damage when injected to animals. HHT® contains 3.0 mg of metacresol, a concentration widely used by other somatropin products, and which was demonstrated as safe and well tolerated in several studies.

4.5. Interaction with other medicinal products and other forms of interaction

The concomitant administration of glucocorticoids may inhibit HHT® effect on growth (apart from reducing the endogenous production of growth hormone). In case of associated adrenocorticotropic hormone (ACTH) production deficit, the eventual treatment should be adjusted with glucocorticoids in order to minimize the inhibitory effect on growth.

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

There is preliminary evidence of the somatropin-related regulation of several cytochrome P 450 isoforms. Growth hormone may potentially alter the metabolism of some drugs which are metabolized 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.

Somatropin interacts with oral estrogens. In patients on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal. Contrarily, if a woman on somatropin discontinues oral estrogen treatment, she might reduce the somatropin dosage to avoid the growth hormone excess and/or adverse effects. It seems that men show an increment of IGF-1 sensitivity with time. This means that men are at risk of receiving an excess treatment.

Growth hormone and somatropin inhibit the microsomal enzyme 11β hydroxysteroid dehydrogenase-1 (11βHSD-1), required for conversion of cortisone to its active metabolite, cortisol. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Introduction of somatropin treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. Consequently, previously undiagnosed secondary hypoadrenalism may be unmasked and it may be necessary to initiate a glucocorticoid replacement therapy in patients on somatropin. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require increased maintenance doses following initiation of somatropin treatment; this may be especially relevant for patients treated with cortisone acetate, meprednisone and prednisone since conversion of these drugs into their biologically active metabolites is dependent on the activity of 11βHSD-1.

Antagonisms and antidotes

Resistance to the action of growth hormone may be observed in patients with hypercatabolic signs, such us the wasting syndrome associated to HIV infection, and in patients with antibodies to-growth hormone. Specific antidotes used today against somatropin are still unknown even though pegvisomant - an antagonist of GH receptor, is used in acromegaly.

4.6. Fertility, pregnancy and lactation

Fertility and pregnancy

FDA Pregnancy Category B (trials performed in animals did not show evidential risk, but there is no data in humans). 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 on the fetus or impairment in fertility.

Breast feeding

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

4.7. Effects on ability to drive and use machines

HHT® has no influence on the ability to drive and use machines.

4.8. Adverse reactions

There follows a list of the most important adverse reactions which are also listed under CONTRAINDICATIONS and PRECAUTIONS:

- Increased fatalities in acute critical disease patients
- Neoplasms
- Death in PWS pediatric patients
- Glucose intolerance and diabetes mellitus
- Intracranial hypertension
- Severe hypersensitivity
- Fluid retention
- Hypothyroidism
- Femoral epiphysis luxation in pediatric patients
- Progression of preexisting scoliosis in pediatric patients
- Otitis media and cardiovascular disorders in Turner syndrome patients
- Lipoatrophy
- Pancreatitis

As for specific populations, the following adverse events have been reported in clinical trials:

In pediatric patients with GHD the following events were rarely reported: injection site reactions, including pain or burning associated with the injection, fibrosis, nodules, skin rash,

inflammation, pigmentation or bleeding; lipoatrophy; headache; hematuria; hypothyroidism; and mild hyperglycemia.

In pediatric PWS patients the following events were reported: edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia.

In clinical studies on pediatric patients born small for gestational age, the following clinically significant events were reported: mild transient hyperglycemia, benign intracranial hypertension, central precocious puberty, jaw prominence, and aggravation of preexisting scoliosis, injection site reactions, and self-limited progression of pigmented nevi.

In pediatric patients with Turner syndrome, the most frequently reported adverse events were respiratory illnesses (influenza, tonsillitis, otitis, sinusitis), joint pain, and urinary tract infection.

In pediatric patients with idiopathic short stature, the most frequently reported adverse events were upper respiratory tract infections, influenza, tonsillitis, nasopharyngitis, gastroenteritis, headaches, increased appetite, pyrexia, fracture, altered mood, and arthralgia.

In adult patients with GHD, most of the adverse events were mild to moderate symptoms of fluid retention, including peripheral edema, arthralgia, pain and limb stiffness, myalgia, paresthesia, hypoesthesia, fatigue, back pain, Diabetes Mellitus, carpal tunnel syndrome.

The prolonged use of excessive doses of human growth hormone in patients with no GHD might result in acromegaly trails in face, hands, feed and other related clinical signs including visceromegaly, diabetes, atherosclerosis, arterial hypertension and carpal tunnel syndrome.

The development of antibodies to growth hormone may occur in a reduced number of patients. Interference with response to treatment in terms of growth has been described only when their binding capacity exceeds 2 mg/l.

The reported adverse events of frequent incidence included otitis media or hearing disorders in Turner syndrome patients. During somatropin treatment the following adverse events were reported infrequently: carpal tunnel syndrome, gynecomastia, headache, increase of nevi, articular and muscle pain, peripheral edema, general weakness, skin allergic reactions (rash), jaundice, intracranial hypertension (blurred vision, headache, nausea, emesis,

papilledema) and lipodystrophy at the injection site which can be diminished by rotation of the site of injection.

Intracranial hypertension symptoms usually occur within the first 8 weeks of treatment and disappear with dose reduction of therapy discontinuation.

Adverse events in special populations

Children

Infrequent reactions in the site of injection (with pain, swelling, burning 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 either caused by growth hormone or not were: 1) Infections (especially *Pneumocystis carinii*). 2) Kaposi's Sarcoma. 3) Edema. 4) Neurological conditions: paresthesia, headaches, seizures, hypertonia, nystagmus, meningeal symptoms, tremor. 5) Respiratory disorders: dyspnea, cough, sinusitis, infections of the upper respiratory tract, pharyngitis, rhinitis, pneumonia, bronchitis, pleurisy. 6) Gastrointestinal disorders: abdominal pain, gingivitis, gastritis, diarrhea, dyspepsia, pancreatitis, hepatitis, lithiasic cholestasis. 7) Hematologic disorders: lymphadenopathy, eosinophilia, thrombocytopenia. 8) Carpal tunnel syndrome. 9) Skin disorders: rash, pruritus, hyperpigmentation, folliculitis, acne, alopecia, pain on the injection site, ulcers on the skin. 10) Psychiatric disorders: depression, anxiety, somnolence, thought disorders. 11) Ocular disorders: retinitis, photophobia. 12) Hepatic function disorders. 13) Gynecomastia and pain in the mammary gland 14) Hearing disorders. 15) Cardiovascular disorders: precordial pain, hypertension and hypotension, ECG abnormalities, cardiac murmur. 16) Alterations on lab tests: increase of triglycerides, 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 myalgias and the diarrhea were more frequent in the treated patients than in those who were not treated. Development of specific antibodies was not observed.

Reporting of suspected adverse events

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system or to the Drug Safety Unit of BIOSIDUS S.A.: Constitución 4234 (C1254ABX) Buenos Aires, Argentina. (54-11) 4909-8048. farmacovigilancia@biosidus.com.ar.

4.9. Overdose

No data of HHT® overdose is available; however, some isolated cases have been reported after using some other somatropin preparations. The clinical effects caused by overdose in such cases included:

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 the size of head, hands and feet, articular and limb pain, polyuria, polydipsia).

In case of an overdose, go to the nearest hospital or phone the following toxicology centers.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anterior pituitary lobe hormones and analogues; ATC code: H01A C01.

HHT® is a biosimilar medicinal product.

Mechanism of action

Somatropin, as well as endogenous GH, exerts its action by binding to specific receptors on the surface of several cells. The activation of these receptors triggers a tandem of intracellular events, mainly phosphorylations, which end up on the regulation of several gene expressions at the transcription level. Most of somatropin anabolic effects are mediated by IGF-I, which is synthesized by 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 achieve normal levels following somatropin treatment.

Pharmacodynamic effects

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 with 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 increase their 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 level. In GHD adults, somatropin treatment reduces the adipose tissue, increases the muscular mass, produces metabolic alterations including beneficial changes on the lipid metabolism and leads IGF-I concentrations to normal levels.

Somatropin stimulates growth in humans and exerts other actions such as:

- On the glucidic metabolism, it reduces the tolerance to carbohydrates. Pediatric patients with hypopituitarism and GHD -mainly during the neonatal period, may experience hypoglycemia when fasting, which can be reverted by somatropin treatment. High HHT® doses or its use in healthy individuals may alter tolerance to glucose.

- On lipid metabolism, it has lipolytic effect. In GHD patients, somatropin administration causes lipid mobilization, reducing the body fat and increasing free fatty acids levels in plasma.

- On protein metabolism, it exerts anabolic effect. The lineal growth partly includes through the increase of the protein synthesis at cellular level. At somatropin-therapy onset, retention and further decrease of nitrogen excretion at urinary level occur.

- On electrolytic metabolism, somatropin induces the retention of sodium, potassium, water and phosphorus. In GHD patients, the serum concentration of inorganic phosphate is

increased following somatropin treatment. Serum calcium does not show meaningful disorders as a result of somatropin treatment, probably causing a transient increase at treatment onset (throughout the first 6-month period), reflecting an increase over the bone turnover because of growth. Growth hormone may transiently increase calciuria (around the third month of treatment) with subsequent decrease.

- On bone growth, somatropin stimulates such growth in pediatric patients with GHD, Turner syndrome, intrauterine growth retardation with no pondostatural gain and PWS. Body length increase is the result of somatropin effect on the epiphysiary plates of long bones. IGF-I concentrations, which play a very important role in bone growth, are low in GHD pediatric patients, but they increase under somatropin treatment, as well as alkaline phosphatase serum level (bone growth marker).

- On body composition, GHD adult patients on somatropin treatment at recommended doses showed a decrease of the body adipose mass and an increase of the lean mass.

5.2. Pharmacokinetic properties

Absorption

Eighty per cent of somatropin is absorbed when injected by subcutaneous route. Using HHT®, maximum plasma concentration is achieved approximately 3.27 ± 1.08 hours following SC administration in healthy volunteers, with an absorption half-life of around 0.75 hours. Following HHT® administration at 4 IU, plasma peak (as geometric mean and 95% confidence interval) in adult healthy volunteers was 8.32 ± 3.42 mg/ml.

Distribution

The apparent distribution volume of somatropin following administration of HHT® at 4 IU doses to healthy volunteers is 139.10 ± 69.45 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 enrolling healthy volunteers following the administration of HHT® 4 IU, the elimination half-life HL Lambda was 4.22 ± 1.59 hours. In

healthy volunteers serum concentrations of HHT® decrease following SC injection showing half-life of approximately 6 hours.

Duration of action

Approximately between 12 and 48 hours.

Specific populations and genre

No pharmacokinetic studies of HHT® have been performed on pediatric patients. For GHD adults, it has been reported that somatropin bioavailability was similar in men and women.

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lyophilized powder contains:

Glycine

Mannitol

Anhydrous sodium dibasic phosphate

Anhydrous sodium monobasic phosphate

Each pre-filled syringe with diluent contains:

Distilled water for injection.

Each ampoule with diluent contains:

Distilled water for injection

m-Cresol

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

A shelf life of 24 months is established when the product is stored under authorized storage conditions (see section 6.4).

Shelf life after reconstitution

After reconstitution, immediate use is recommended.

However, HHT® can be used within the 3 subsequent weeks, keeping it refrigerated between 2 °C and 8 °C, in its original package.

6.4. Special precautions for storage

HHT® should be stored in the refrigerator between 2 °C and 8 °C, protected from light.

Do not freeze.

In case of freezing, discard the product.

6.5. Nature and contents of container

The lyophilized powder (corresponding to 16 I.U.) is contained in a neutral, transparent glass vial (type I), with a slotted grey stopper (butyl), silver seal (aluminum) and a flip-off closure (lilac plastic cover).

The solvent (1 mL) is contained in a transparent glass ampoule.

HHT® is authorized in the following presentations:

HHT® 16 I.U.:

- Pack with 1 vial with lyophilized powder + 1 ampoule with solvent.

Not all presentations or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling of products

Reconstitute the content of an HHT® vial with one milliliter of water for injection from the prefilled syringe or ampoule with diluent, making it flow against the vial wall. After reconstitution, swirl the vial with a soft rotary motion until the content is completely dissolved.

Do not shake the solution during preparation.

Before puncturing the stopper, it should be cleaned with isopropyl alcohol in order to avoid contamination.

The solution after reconstitution is clear and colorless and should not have visible particles or lumps.

The following is a general description of the reconstitution and administration process:

Step 1: reconstitution of the freeze-dried powder.

• Clean the rubber stopper of the vial with the isopropyl alcohol wipe.

• Carefully open the blister of the thicker needle and place it in the luer lock of the syringe.

• Puncture the rubber stopper and inject the solvent against the glass wall of the vial.

• Do not inject the liquid directly on the powder.

• Once the solvent syringe has been emptied, gently rotate the vial in circles until the powder and the solvent are thoroughly mixed.

• Do not shake the vial to mix the solution.

• Pull the syringe plunge and withdraw the full vial content.

Step 2: prepare the injection.

• Remove the thick needle from the syringe and replace it by the small needle.

• Place the syringe in vertical position (needle upwards) and tap gently.

• Then, slightly press the plunger, remove any air bubble in the vial.

• Clean the injection site with the cotton wipe or gauze embedded in alcohol.

• Grasp the skin and introduce the needle with the syringe perpendicular to skin

• Inject the content of the syringe by pressing the plunger until it tops

• Remove the syringe.

• Discard all the remains properly.

Medications should not be disposed of through drains or trash. Doctors and pharmacists should explain to patients how to dispose of containers and medications that they no longer need. This way they will help to protect the environment.

7. MARKETING AUTHORIZATION HOLDER

BIOSIDUS S.A.

Administration and Laboratories: Constitución 4234, (C1254ABX) Ciudad Autónoma de Buenos Aires.

Industrial facilities: Av. Los Quilmes 137, Bernal, Provincia de Buenos Aires.

República Argentina

8. NUMBERS OF MARKETING AUTHORIZATION

Medicinal specialty authorized by the Ministry of Health of the Argentine Republic.

Certificate N° 46,109.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 11th April 1997 (Argentina).

Date of last renewal: 11th April 2017 (Argentina).

10. DATE OF REVISION OF THE TEXT

The information contained in this document was last updated in August, 2020.