Application for a Marketing Authorization

Somatropin, rDNA origin (rhGH)

JINTROPIN® for injection

SmPC

Changchun GeneScience Pharmaceutical Co., Ltd.

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1. Trade Name of the Medicinal Product

JINTROPIN

2. Qualitative and Quantitative Composition

Lyophilized powder containing labelled IU amount of human growth hormone (somatropin).

3. Pharmaceutical Form

Lyophilized powder to be used s.c after reconstitution with 1ml water for injection.

4. Clinical Particulars

4.1 Therapeutic Indications

- ✓ Pediatric growth retardation due to inadequate secretion of endogenous GH.
- ✓ Severe burns.
- ✓ Growth hormone deficiency (GHD) due to diseases of hypothalamus-pituitary gland, or as diagnosed by 2 independent GH stimulation tests.

4.2 Posology and Method of Administration

- ✓ Before administration, add 1ml of WFI to the rhGH vial of lyophilized powder, and make the solvent run slowly down the side of the vial. Swirl the vial with a gentle rotary motion until contents are dissolved completely. Do not shake vigorously. Immediately used after dissolving.
- ✓ The dose of administration should be individual for each patient. For growth-promotion purpose in children, the recommended dose is 0.1-0.15IU/kg/day, once per day, subcutaneous injection. The period of treatment is from 3 months to 3 years. Or follow your physicians' prescription.
- ✓ For severe burn patients, a daily dose of 0.2-0.4IU/kg subcutaneous injection is recommended. The period of treatment is about 2 weeks.
- ✓ The dose might require adjustment individually for human replacement therapy. Generally the dose is from small dose, e.g., 0.5IU (0.17mg)/day or up to 0.02IU/kg/day, it is equal to 0.007mg/kg/day; after 1-2 months treatment, the dose might be modulated gradually to 0.04IU/kg/day, it is equal to 0.013mg/kg/day. The daily dose should then be modulated according to the determination of Insulin-like Growth Factor-I (IGF-I) in serum. The dose may decrease with age increasing.

4.3 Contraindications

Jintropin should not be administered to patients with known hypersensitivity to growth hormone.

Jintropin should not be administered to pregnant women, to nursing mothers.

Incompatibilities have not been reported for combined use of JINTROPIN with other medicaments or medical solution.

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

Somatropin is contraindicated in patients with proliferative or preproliferative diabetic retinopathy.

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Sincegrowth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of somatropin treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

Somatropin should not be used to treat patients who have acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure.

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment. Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, somatropin is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

4.4 Special Warnings and Precautions for Use

The diagnosis should be confirmed before treatment starts. Therapy with Jintropin should be prescribed directly by qualified physicians. In diabetes mellitus, the dose of insulin might require adjustment by your physician before JINTROPIN treatment starts.

Experience in adult GHD patients above 60 years is lacking.

Experience with prolonged treatment in adults is limited.

In chronic renal insufficiency the renal function should be investigated before start of the treatment. The treatment should be discontinued after renal transplantation.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products.

Progression of scoliosis can occur in patients who experience rapid growth.

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders

Patients should be monitored carefully for any malignant transformation of skin lesions.

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site.

As with any protein, local or systemic allergic reactions may occur. Parents/Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

Progression of scoliosis can occur in patients who experience rapid growth.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

Simultaneous glucocorticoid therapy might inhibit the effect of hGH. Generally, the dose of glucocorticoid can not exceed 10-15mg CORT/m^2 of surface areas. Growth rate can be increased by the combination with other non-androgen steroids.

4.6 Pregnancy and Lactation

The use of Jintropin during pregnancy is not known. The safety of Jintropin for use in human pregnancy has not been established (Category B3).

Jintropin is not studied in nursing mothers. Information is lacking whether peptide hormones pass over into the breast milk but absorption in the gastro-intestinal tract of the infant of intact protein is extremely unlikely.

4.7 Effects on Ability to Drive and Use Machines

The ability to react during machine operation or drive is not shown to be influenced by Jintropin.

4.8 Undesirable Effects

Oedema and headache may occur, particularly on commencement of treatment.

JINTROPIN may cause elevated serum glucose levels, which will usually return to normal after continual uses, or stop using.

In clinical trials in adults side effects have been noted in approximately 30 to 40% of the patients, primarily related to symptoms of fluid retention (oedema). These events have an early onset after initiation of therapy, but with a reduction in incidence and prevalence over time and rarely influencing daily activities.

JINTROPIN has shown to give rise to the formation of antibodies in very few patients. This has no influence on the treatment result.

It has been reported that patients may develop hypothyroidism during treatment with JINTROPIN which should be considered by your physician.

If nausea and/or vomiting, severe and recurrent headache especially in combination with visual problems occur take contact with your physician.

Injection site pain was reported infrequently.

A mild and transient edema was observed early during the course of treatment.

Scoliosis, otitis media, hyperlipidemia, gynecomastia, hypothyroidism, aching joints, hip pain, arthralgia, arthrosis, myalgia, hypertension were observed.

4.9 Overdose

Overdosage with Jintropin has not been well studied. No effect of overdose or intoxication is known.

If an overdose of JINTROPIN has been injected, contact your physicians immediately.

According to previous reports, acute overdosage of somatropin could lead to initial hypoglycaemia followed by hyperglycemia. Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human GH.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

It has been demonstrated that somatropin is therapeutically equivalent to pituitary-derived human GH (hGH). Pediatric patients who lack adequate endogenous GH secretion. Patients treated with Jintropin resulted in an increase in growth rate and an increase in insulin-like growth factor-I (IGF-I) levels similar to that seen with hGH.

Similar actions that have been demonstrated for Jintropin and hGH include:

A. Tissue Growth

1) Skeletal Growth: GH stimulates skeletal growth in pediatric patients with growth retardation due to a lack of adequate secretion of endogenous GH. Skeletal growth is accomplished at the epiphyseal plates at the ends of a growing bone by GH and one of its mediators, IGF-I. This results in linear growth until these growth plates fuse at the end of puberty.

2) Cell Growth: Treatment with hGH results in an increase in both the number and the size of skeletal muscle cells.

3) Organ Growth: GH influences the size of internal organs and increases red cell mass.

B. Protein Metabolism

Linear growth is facilitated in part by GH-stimulated protein synthesis, which is demonstrated by nitrogen retention during GH therapy.

C. Carbohydrate Metabolism

Patients with fasting hypoglycemia could be improved by treatment with GH. Jintropin therapy may decrease insulin sensitivity. Administration of hGH resulted in increases in serum fasting and postprandial insulin levels.

D. Lipid Metabolism

Administration of somatropin resulted in lipid mobilization, reduction in body fat stores, increased plasma fatty acids, and decreased plasma cholesterol levels.

E. Mineral Metabolism

Serum levels of inorganic phosphorus may increase slightly in patients with inadequate endogenous GH. Sodium retention may occur.

F. Connective Tissue Metabolism

Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

5.2 Pharmacokinetic Properties

Following s.c. administration of 0.1 mg/kg of JINTROPIN, the elimination half-life was about 3.01 hours (hrs) for first dose (FD) and 2.77 hrs for repeating multiple doses (MD) in healthy volunteers. The elimination rate: 0.23±0.04 (FD) and 0.25±0.04/hr (MD), and the Absorption Rate: 0.43±0.05 (FD) and 0.48±0.04/hr (MD), the Clearance of Sera (CL/F): 0.32±0.02 (FD) and 0.54±0.09L/hr.kg (MD).

6. Pharmaceutical Particulars

6.1 List of Excipients

Glycine, sucrose, Tween-80, L-methionine, sodium dihydrogen phosphate, disodium hydrogen phosphate.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Shelf life of the product as packaged for sale:

Primary packaging material	Shelf life
2ml glass vial sealed with aluminium caps. A pack may contain 5, 10 or 20 vials with indicated IU amount. To be stored in 2-8℃ under refrigerator.	36 month

6.4 Special Precautions for Storage

The product should be protected from strong light. Avoid freezing.

Before Reconstitution – JINTROPIN Vials are stable under refrigeration at 36-46°F (2-to 8°C). Expiration dates are stated on the labels.

6.5 Nature and Contents of Container

Calendar packs, each containing 5, 10 or 20 glass vials

6.6 Instructions for Use/Handling

Jintropin must not be used after the expiry date.

Keep out of the reach of children.

Occasionally, after refrigeration, some cloudiness may occur. This is not unusual for protein drugs like JINTROPIN growth hormone. Allow the product to warm to room temperature. If cloudiness persists or particulate matter is noted, the contents MUST BE DICARDED.

The septum of the vial should be wiped with rubbing alcohol or an alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions. It is recommended that JINTROPIN be administered with sterile disposable syringes and needles. The syringes should be of small enough volume with reasonable accuracy.

7. Marketing Authorisation Holder

Changchun GeneScience Pharmaceutical Co., Ltd. (GenSci), 1718 Yueda Road, Changchun High-tech development zone, Jilin 130012, China

8. Marketing Authorisation Number

CHINA

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9. Date of First Authorisation/Renewal of Authorisation

September 30, 1998/September 29, 2010

10. Date of Partial Revision of the Text

January 15, 2007