Growth Hormone Deficiency (GHD)

"What may help my child grow?"
"What is GHD?"
"What causes GHD?"
"How can GHD be treated?"

Your questions answered.

ZOMACTON® (somatropin) for Injection
for Pediatric Growth Hormone Deficiency

Indication

ZOMACTON® (somatropin) for Injection is a human growth hormone prescription medication for:

- Treatment of pediatric patients who are not growing because they do not make enough growth hormone on their own.
- Replacement of growth hormone in adults who do not make enough on their own.

Important Safety Information

WHO SHOULD NOT TAKE ZOMACTON®?

ZOMACTON® is not for:

- Patients who have acute critical illness after heart or abdominal surgery, multiple trauma or acute severe breathing problems.

Please see additional Important Safety Information throughout this brochure and accompanying full Prescribing Information.

ZOMACTON®
(somatropin) for Injection
5mg and 10mg

Understanding
Growth Hormone Deficiency

A diagnosis of growth hormone deficiency (GHD) can come with so many questions for you and your child. But it's also an answer. And once you understand more about GHD, its causes, and how you can treat it, you can begin to feel more confident that you're armed with the knowledge, treatment, and support you need to help your child on the journey to growth.

"How does a body grow?"

The Endocrine System, Glands, and Hormones

To help you understand the growth process, here is a simple description of what goes on inside a child's body to make it grow.

Growth (along with many other functions) is controlled by the endocrine system. The endocrine system is a network of glands and organs that communicate with each other—and with the rest of the body—by releasing chemicals called hormones.[1]

The pituitary gland is a pea-sized organ near the base of the brain. It is often called the "master gland" because it produces many hormones that control various processes in the body. The pituitary gland produces growth hormone (GH).[1,2]

GH plays an important role in the body, especially in developing children. It's key to normal growth and metabolism.[3]

How GH Affects Growth

GH triggers the release of insulin-like growth factor-1 (IGF-1). This hormone circulates throughout the body and causes cartilage cells to grow, which results in bone growth. It also promotes the growth of muscle and other tissues.[3]

How GH Affects Metabolism

Metabolism is the body's natural process of converting food into energy and waste products. GH affects this process in several ways. It encourages the body to use more amino acids, which creates more proteins. It helps maintain proper levels of carbohydrates in the body and stimulates the use of fat (stored energy) by breaking down triglycerides.[3]

"Why do some bodies not grow properly?"

Defining Growth Hormone Deficiency

Simply put, a child with GHD is not producing enough growth hormones for normal development. GHD is a condition that affects both boys and girls. In fact, there is an estimated 1 in 4,000 to 10,000 children who have GHD.[4]

GHD may occur by itself or in combination with other hormone deficiencies. And there are different degrees of GHD. **Total GHD** means that no growth hormone is produced at all. If some growth hormone is produced, but not enough for normal growth, it is called **partial GHD**.[5]

Some causes of GHD are **Congenital**, **Acquired**, and **Other**.

Congenital GHD

"Congenital GHD" means that the child has been born with this condition. From birth, the endocrine system doesn't work properly to encourage normal growth. This *may* be the result of something that happened while the child was in the womb, such as an injury or other complication. Congenital GHD may not be noticeable for months.[5]

Acquired GHD

Damage to the pituitary gland or other important parts of the endocrine system after birth can result in "acquired GHD." Serious illness, exposure to radiation therapy, or a head injury can result in GHD at any time. Often, a tumor affecting the hypothalamus or pituitary gland will cause acquired GHD. But even if the tumor is removed, it may not correct the degree of GHD.[5]

Other Impacts on Growth

There are other factors besides GHD that may impact a child's growth. Poor nutrition, more than anything, may prevent a child from growing at a normal rate. A balanced diet is essential to the healthy development of growing children. However, even if a child eats a balanced diet, growth problems can still occur if the food is not absorbed and metabolized properly.[5,6]

Discovering Treatment Options

Remember: Although in many cases no cause can be found for GHD, now you can get help—by working with your doctor to get the proper treatment and support.

"How can growth hormone replacement therapy help?"

Your Doctor Has Recommended Growth Hormone Replacement Therapy

You and your doctor have decided to treat your child's Growth Hormone Deficiency (GHD) with ZOMACTON® (somatropin) for Injection. ZOMACTON® is a prescription growth hormone product for the treatment of growth failure in children who do not make enough growth hormone on their own.

Since 1988, ZOMACTON® has been approved in 47 countries around the world to treat GHD.

With human growth hormone (hGH) therapy like ZOMACTON®, your child may reach a height similar to that of other children his or her age. Not everyone responds to hGH therapy in the same way. However, today most children receiving replacement therapy reach a normal adult height consistent with the average height of others in their family. The sooner your child begins treatment, the more successful therapy is likely to be.[4,5]

ZOMACTON®
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Beginning GH Therapy

GH therapy with ZOMACTON® only works when injected. Your doctor will prescribe injections for your child, based on weight, that can be given three (3), six (6), or seven (7) times a week.

The recommended weekly dose in milligrams (mg) per kilogram (kg) of body weight for pediatric patients is 0.18 mg/kg/week to 0.3 mg/kg/week (0.026 mg/kg/day to 0.043 mg/kg/day). **Please refer to the ZOMACTON® Prescribing Information or your doctor for complete dosing information.**

ZOMACTON® is available in 5-mg and 10-mg vials. Your doctor will decide whether 5 mg or 10 mg will be best for your child.

Select Important Safety Information

WHO SHOULD NOT TAKE ZOMACTON®?

ZOMACTON® is not for:

- Patients who have acute critical illness after heart or abdominal surgery, multiple trauma or acute severe breathing problems.
- Pediatric patients with Prader-Willi syndrome who are severely overweight, have sleep apnea or a history of or existing severe breathing problems due to risk of death.
- Patients who have active cancer.
- Patients who are allergic to any of the ingredients provided with ZOMACTON®.
- Patients with severe visual problems caused by diabetes.
- Pediatric patients whose growth plates have closed.

Please see Important Safety Information throughout this brochure, and accompanying full Prescribing Information.

"What if I have questions about treatment or insurance?"

The ZoGo Support Program Can Help

ZoGo SUPPORT PROGRAM

When you choose ZOMACTON® (somatropin) for Injection, you're not only getting a GH therapy with an established track record, you're also getting all the support you need throughout treatment with ZoGo, your personalized support program.

Your doctor's office staff will enroll eligible patients in the ZoGo Support Program and let the ZoGo team know your child is being prescribed ZOMACTON®. Our team of professionals is with you every step of the way, 24 hours a day, 7 days a week. Patients must meet eligibility requirements to access certain Program benefits. Please contact the ZoGo Support Program at 844-944-ZOGO (9646). You'll get a welcome phone call to answer any immediate questions and a complete Welcome Kit with tools and information about GH therapy and ZOMACTON®. In addition, one of our specially trained nurses will come to your home to teach you and/or your child's caregiver how to safely and correctly give your child ZOMACTON® injections.

But it doesn't stop there. The ZoGo Support Program team will help make sure your shipment of ZOMACTON® is received and even coordinate insurance coverage with your pharmacy. There are also special ZOMACTON® financial assistance programs that you may qualify for as well. The ZoGo Support Program team can help you with that, too.

Throughout treatment, the ZoGo Support Program team will continue to be your contact for information, insurance coverage, and refills. Thanks to ZoGo, with ZOMACTON® treatment you'll never have to go it alone.

Please see Important Safety Information throughout this brochure, and accompanying full Prescribing Information.

"What should we expect from GH therapy?"

Treatment With ZOMACTON® (somatropin) for Injection

Your physician will monitor your child's response to ZOMACTON®. It's possible your child may experience side effects; if he or she does experience any side effects, you should talk to your doctor immediately. We've included Important Safety Information throughout this brochure. You can also refer to the accompanying full Prescribing Information.

The First Few Months

As your child begins treatment, there is sometimes a sudden "spurt" in growth rate. This fast increase may be noticeable to you and your child within 3 to 4 months. Eventually, growth should progress more slowly, but remain steady.[5]

Stay the Course

If this sudden growth spurt doesn't occur, or once it has tapered off, you and your child may become impatient and expect faster results. Don't become discouraged or give up. Stay on track. Stick to the plan and dosing schedule provided by your doctor. **NEVER** increase the dose or number of injections unless specifically instructed to do so by your doctor.

Be Positive

You should see results over time. But, remember that growth is a slow process measured over many months and possibly years. If your child expects to grow suddenly overnight after starting treatment, he or she will be disappointed. Your doctor will discuss realistic short- and long-term expectations with you and will determine how long your child will remain on GH. Treatment may last into the late teens or early adulthood. It's important that you explain all of this to your child, and remind your child (and yourself) to be patient.[5] Good communication during this journey is crucial to help your child keep a positive outlook.[5]

Please see Important Safety Information throughout this brochure, and accompanying full Prescribing Information.

"How can I help my child throughout treatment?"

Positive Support for Children With GHD

Remember, smaller doesn't mean younger. And just because your child is small in size doesn't mean he or she should be treated as if he or she was younger. For children with GHD to mature and grow emotionally, they need to be treated like children their own age. This can sometimes be hard for other children, and even adults may treat a small child as if he or she was younger. It's important for you to talk to your child about this. Provide encouragement, praise any accomplishments, and boost your child's confidence whenever you can. It's also important to talk to your child's teachers and classmates. Help them understand a little bit about GHD, and ask for their help in keeping your child positive.

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Getting the Results

Treatment for children with GHD is a journey. It's not always easy for them, or for you. But, if you and your child can keep a positive attitude, the results may be satisfying. For more information, visit zomacton.com or call 1-844-944-ZOGO (9646).

Please see Important Safety Information throughout this brochure, and accompanying full Prescribing Information.

References

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3. Bowen RA. The hypothalamus and pituitary gland: introduction and index. In: Bowen RA, Austgen L, Rouge M, eds. *Pathophysiology of the Endocrine System.* http://arbl.cvmbs.colostate.edu/hbooks/pathphys/endocrine/hypopit/. Accessed February 16, 2017.
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6. The Magic Foundation. What causes children to grow poorly? https://www.magicfoundation.org/Growth-Disorders/. Accessed February 16, 2017.

ZOMACTON® (somatropin) for Injection
IMPORTANT SAFETY INFORMATION *(continued)*

- Pediatric patients with Prader-Willi syndrome who are severely overweight, have sleep apnea or a history of or existing severe breathing problems due to risk of death.
- Patients who have active cancer.
- Patients who are allergic to any of the ingredients provided with ZOMACTON®.
- Patients with severe visual problems caused by diabetes.
- Pediatric patients whose growth plates have closed.

WHAT SHOULD I TELL MY DOCTOR BEFORE OR WHILE TAKING ZOMACTON®?

- If you have or had cancer as a child. Tell your doctor if you experience changes in behavior, headaches, problems with vision, changes in skin coloration or changes in pre-existing moles/birthmarks.
- If you have diabetes, pre-diabetes, or risk factors for diabetes. All patients should have periodic blood sugar monitoring during ZOMACTON® treatment. New cases of type 2 diabetes mellitus have been reported.
- If you have any visual changes, headache, nausea, and/or vomiting while taking ZOMACTON®. This may be a sign of increased pressure in the brain. Routine eye exams should be performed by your doctor.
- If you are allergic to somatropin or any of its ingredients. Seek prompt medical attention if you experience an allergic reaction.
- If you are retaining water during treatment. This may frequently occur, be brief and dose dependent.
- If you have hypoadrenalism and are receiving glucocorticoid replacement therapy. Your doctor may need to adjust the dose of your medication.
- Thyroid function should be checked periodically. Thyroid hormone replacement may need to be started or adjusted during ZOMACTON® therapy.
- If you develop a limp or have hip or knee pain during ZOMACTON® treatment. A fracture in the ball of the hip joint can occur in pediatric patients who have rapid growth.
- If you have scoliosis. Progression of existing scoliosis can occur and should be monitored during treatment in pediatric patients who have rapid growth.
- If you have abdominal pain. Cases of pancreatitis have been reported in patients and may be greater in pediatric patients receiving somatropin.
- If patient receiving ZOMACTON® 5 mg is a newborn or an infant. ZOMACTON® 5 mg includes a diluent that contains benzyl alcohol which can cause serious and fatal reactions. Mix with normal saline, instead of the diluent provided containing benzyl alcohol, when administering to newborns or infants.

Important Safety Information (continued)

- You should rotate your injection sites to avoid breakdown of skin.
- If you are taking any other medications because they may affect each how each other works. Your doctor may adjust the dose of ZOMACTON® or of the other medications you are taking.
- If you are pregnant or nursing. If ZOMACTON® 5 mg is needed while pregnant or nursing, it should be mixed with normal saline or use ZOMACTON® 10 mg, which contains a benzyl alcohol-free formulation.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ZOMACTON®?

The most common side effects include upper respiratory infection, fever, sore throat (pharyngitis), headache, earache (otitis media), swollen hands/feet or ankles (edema), joint or muscle pain/discomfort (arthralgia, paresthesia, myalgia), runny or stuffy nose (rhinitis), back pain, flu symptoms, and changes in liver function (AST).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 800-FDA-1088.

HOW SHOULD I STORE ZOMACTON®?

ZOMACTON® must be kept refrigerated (36° to 46°F [2° to 8°C]). DO NOT FREEZE. After mixing with liquid, ZOMACTON® 5 mg must be used within 14 days and ZOMACTON® 10 mg must be used within 28 days. Do not use if it has expired. Do not inject medication if it is cloudy.

Please see accompanying Full Prescribing Information for ZOMACTON®.

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The individuals depicted are models, not actual patients.

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FERRING
PHARMACEUTICALS

All adverse reactions with ≥5% overall occurrence rate during 12 or 18 months of replacement therapy with another somatropin product are shown in Table 2 (adult-onset patients) and in Table 3 (childhood-onset patients).

Adult patients treated with another somatropin product who had been diagnosed with GH deficiency in childhood reported adverse reactions less frequently than those with adult-onset GH deficiency.

Table 2: Adverse Reactions Occurring ≥5% in Adult-Onset Growth Hormone-Deficient Patients Treated with Another Somatropin Product for 18 Months as Compared with 6-Month Placebo and 12-Month Exposure to Another Somatropin Product[a]

Adverse Reaction	18 Months Exposure [Placebo (6 Months)/GH (12 Months)] (N=46) (%)	18 Months GH Exposure (N=52) (%)
Edema[b]	15	21
Arthralgia	15	17
Paresthesia	13	17
Myalgia	13	14
Pain	13	14
Rhinitis	11	14
Peripheral edema[c]	17	12
Back pain	11	10
Headache	11	8
Hypertension	4	8
Acne	0	6
Joint disorder	2	6
Surgical procedure	2	6
Flu syndrome	7	4

[a] Abbreviations: GH=another somatropin product; N=number of patients receiving treatment in the period stated;
[b] p=0.04 as compared to placebo (6 months).
[c] p=0.02 as compared to placebo (6 months).

Childhood-Onset GH Deficiency
Two double-blind, placebo-controlled trials were conducted in 67 adult patients who had received previous somatropin treatment during childhood. Patients were randomized to receive either placebo injections or another somatropin product (0.00625 mg/kg/day for the first 4 weeks, then 0.0125 mg/kg/day thereafter) for the first 6 months, followed by open-label use of another somatropin product for the next 12 months for all patients. The patients in these studies reported side effects less frequently than those with adult-onset GH deficiency. During the placebo-controlled phase (first 6 months) of the study, elevations of serum glutamic oxaloacetic transferase were reported significantly more often for somatropin-treated (12.5%) than placebo-treated patients (0.0%, p=0.031). No other events were reported significantly more often for somatropin-treated patients during the placebo-controlled phase.

Table 3: Adverse Reactions Occurring ≥5% in Childhood-Onset Growth Hormone-Deficient Patients Treated with Another Somatropin Product for 18 Months as Compared with 6-Month Placebo and 12-Month Exposure to Another Somatropin Product[a]

Adverse Reaction	18 Months Exposure [Placebo (6 Months)/GH (12 Months)] (N=35) (%)	18 Months GH Exposure (N=32) (%)
	%	%
Flu syndrome	23	16
AST increased[b]	6	13
Headache	11	9
Asthenia	3	6
Cough increased	0	6
Edema	9	6
Hypesthesia	0	6
Myalgia	6	6
Pain	9	6
Rhinitis	6	6
ALT increased	6	6
Respiratory disorder	6	3
Gastritis	6	0
Pharyngitis	14	3

[a] Abbreviations: GH=another somatropin product; N=number of patients receiving treatment in the period stated;
ALT=alanine aminotransferase, formerly SGPT;
AST=aspartate aminotransferase, formerly SGOT.
[b] p=0.03 as compared to placebo (6 months).

In an ongoing post-marketing observational study of treatment with another somatropin product in 3,102 GH-deficient adults, hypertension, dyspnea, and sleep apnea were reported by 1% to less than 10% of patients after various durations of treatment.

6.2 Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ZOMACTON in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a clinical trial with another recombinant growth hormone during the first 6 months of somatropin therapy in 314 naive patients, 1.6% developed specific antibodies to somatropin (binding capacity ≥0.02 mg/L). None had antibody concentrations which exceeded 2 mg/L. Throughout 8 years of this same study, two patients (0.6%) had binding capacity >2 mg/L. Neither patient demonstrated a decrease in growth velocity at or near the time of increased antibody production. It has been reported that growth attenuation from pituitary-derived GH may occur when antibody concentrations are >1.5 mg/L.

6.3 Post-Marketing Experience
Because the following adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Severe Hypersensitivity Reactions — Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema
Neurologic — Headaches (common in children and occasional in adults).
Skin — Increase in size or number of cutaneous nevi
Endocrine — Gynecomastia.
Gastrointestinal — Pancreatitis
Metabolic — New-onset type 2 diabetes mellitus
Neoplasia — Leukemia has been reported in a small number of GH deficient pediatric patients treated with somatropin, somatrem (methionylated rhGH), and GH of pituitary origin.

7 DRUG INTERACTIONS
Table 4 includes a list of drugs with clinically important drug interactions when administered concomitantly with ZOMACTON and instructions for preventing or managing them.

Table 4: Clinically Important Drug Interactions with ZOMACTON

Glucocorticoids	
Clinical Impact:	Microsomal enzyme 11ß-hydroxysteroid dehydrogenase type 1 (11ßHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. ZOMACTON inhibits 11ßHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11ßHSD-1 and serum cortisol. Initiation of ZOMACTON may result in inhibition of 11ßHSD-1 and reduced serum cortisol concentrations.
Intervention:	Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of ZOMACTON.
Examples:	Cortisone acetate and prednisone may be effected more than others since conversion of these drugs to their biologically active metabolites is dependent on the activity of 11ßHSD-1 *[see Warnings and Precautions (5.8)]*.
Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment	
Clinical Impact:	Pharmacologic glucocorticoid therapy and supraphysiologic glucocorticoid treatment may attenuate the growth promoting effects of ZOMACTON in pediatric patients.
Intervention:	Carefully adjust glucocorticoid replacement dosing in pediatric patients receiving glucocorticoid treatments to avoid both hypoadrenalism and an inhibitory effect on growth.
Cytochrome P450-Metabolized Drugs	
Clinical Impact:	Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450)-mediated antipyrine clearance. ZOMACTON may alter the clearance of compounds known to be metabolized by CP450 liver enzymes.
Intervention:	Careful monitoring is advisable when ZOMACTON is administered in combination with drugs metabolized by CP450 liver enzymes.
Oral Estrogen	
Clinical Impact:	Oral estrogens may reduce the serum IGF-1 response to ZOMACTON.
Intervention:	Patients receiving oral estrogen replacement may require greater ZOMACTON dosages *[see Dosage and Administration (2.2)]*.
Insulin and/or Other Hypoglycemic Agents	
Clinical Impact:	Treatment with ZOMACTON may decrease insulin sensitivity, particularly at higher doses.
Intervention:	Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other hypoglycemic agents *[see Warnings and Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
The ZOMACTON 5 mg diluent contains benzyl alcohol, which has been associated with gasping syndrome in neonates. The preservative benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants. If ZOMACTON 5mg is needed during pregnancy, reconstitute with normal saline, use only one dose per vial, and discard the reconstituted product after use, or use a ZOMACTON 10 mg benzyl alcohol-free formulation *[see Warnings and Precautions (5.13) and Use in Specific Populations (8.4)]*.

Limited available data with somatropin use in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes. Animal reproduction studies have not been conducted with ZOMACTON.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risk Summary
The ZOMACTON 5mg diluent contains benzyl alcohol. If ZOMACTON 5mg is needed during lactation, reconstitute with normal saline, use only one dose per vial, and discard after use or use a ZOMACTON 10 mg benzyl alcohol-free formulation *[see Warnings and Precautions (5.13) and Use in Specific Populations (8.4)]*.

There is no information regarding the presence of somatropin in human milk. Limited published data indicate that exogenous somatropin does not increase normal breastmilk concentrations of growth hormone. No adverse effects on the breastfed infant have been reported with somatropin. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOMACTON and any potential adverse effects on the breastfed child from ZOMACTON or from the underlying maternal condition.

8.4 Pediatric Use
Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and infants in the intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 mg/kg/day to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 mmol/L to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

When administering ZOMACTON 5 mg to infants, reconstitute with normal saline, not the diluent provided. Only one dose should be used per vial and the reconstituted product should be discarded after use *[see Warnings and Precautions (5.14)]*.

8.5 Geriatric Use
The safety and effectiveness of somatropin in patients aged 65 years and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to development of adverse reactions. A lower starting dose and smaller dose increments should be considered for geriatric patients *[see Dosage and Administration (2.4)]*.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
ZOMACTON contains somatropin, which is not a controlled substance.

9.2 Abuse
Inappropriate use of somatropin may result in significant negative health consequences.

9.3 Dependence
Somatropin is not associated with drug related withdrawal adverse reactions.

10 OVERDOSAGE
Acute overdosage may lead initially to hypoglycemia and subsequently to hyperglycemia. Long-term overdosage may result in signs and symptoms of gigantism or acromegaly consistent with the known effects of excess endogenous human GH.

11 DESCRIPTION
ZOMACTON (somatropin) for injection, is a recombinant human growth hormone. It is a polypeptide of recombinant DNA origin, has 191 amino acid residues and a molecular weight of about 22,124 daltons. It has an amino acid sequence identical to that of human growth hormone of pituitary origin. ZOMACTON is produced in a strain of *Escherichia coli* modified by insertion of the human growth hormone gene.

ZOMACTON is a sterile, white, lyophilized powder, for subcutaneous use, after reconstitution with the accompanying diluent.

ZOMACTON 5 mg vial contains recombinant somatropin 5 mg and mannitol 30 mg. The 5 mg vial is supplied in a combination package with an accompanying 5 mL vial of diluting solution. The diluent contains bacteriostatic 0.9% sodium chloride injection, USP, (normal saline), 0.9% benzyl alcohol as a preservative, and water for injection.

ZOMACTON 10 mg vial contains recombinant somatropin 10 mg, mannitol 10 mg, disodium phosphate dodecahydrate 3.57 mg, and sodium dihydrogen phosphate dehydrate 0.79 mg. The 10 mg vial is supplied in a combination package with an accompanying 1 mL syringe of diluting solution. The diluent contains bacteriostatic water for injection with 0.33% metacresol as a preservative.

Reconstituted solutions have a pH in the range of 7 to 9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Somatropin binds to dimeric GH receptors located within the cell membranes of target tissue cells. This interaction results in intracellular signal transduction and subsequent induction of transcription and translation of GH-dependent proteins including IGF-1, IGF BP-3 and acid-labile subunit. Somatropin has direct tissue and metabolic effects or mediated indirectly by IGF-1, including stimulation of chondrocyte differentiation, and proliferation, stimulation hepatic glucose output, protein synthesis and lipolysis.

Somatropin stimulates skeletal growth in pediatric patients with GHD as a result of effects on the growth plates (epiphyses) of long bones. The stimulation of skeletal growth increases linear growth rate (height velocity) in most somatropin-treated pediatric patients. Linear growth is facilitated in part by increased cellular protein synthesis.

12.2 Pharmacodynamics
Subcutaneous administration of a single dose of 4 mg ZOMACTON in healthy subjects (n=54) with suppressed endogenous growth hormone results in an increased mean (SD) IGF-1 level from 233 (95) ng/mL predose to maximal level of 414 (120) ng/mL after approx. 24 hours. After 96 hours, the subjects displayed a mean (SD) IGF-1 concentration of 228 (74) ng/mL, comparable to the predose value.

12.3 Pharmacokinetics
Absorption — Somatropin has been studied following subcutaneous, and intravenous administration in adult healthy subjects. After a single dose administration of 4 mg ZOMACTON in healthy subjects (n=54) with suppressed endogenous growth hormone resulted in a mean (SD) Cmax of 38.1 (19.3) ng/mL after approximately 4.5 hours. The absolute bioavailability of somatropin is approximately 70% after subcutaneous.

Distribution — The mean (SD) apparent volume of distribution of somatropin after single dose subcutaneous administration of 4 mg ZOMACTON in healthy subjects is 53.3 (24.6) L.

Elimination

Metabolism — Extensive metabolism studies have not been conducted. The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys.

Excretion — In healthy subjects, mean somatropin clearance is 0.133 L/min following intravenous administration. The mean elimination half-life of intravenous somatropin is 0.42 hours, whereas subcutaneously administered somatropin have mean half-life of 2.3 hours, respectively. The longer half-life observed after subcutaneous administration is due to slow absorption from the injection site. Urinary excretion of intact somatropin has not been measured.

Specific Populations

Geriatric patients — The pharmacokinetics of somatropin have not been studied in patients greater than 65 years of age.

Pediatric patients — The pharmacokinetics of somatropin in pediatric patients are similar to those of adults.

Male and Female Patients — No gender-specific pharmacokinetic studies have been performed with somatropin. The available literature indicates that the pharmacokinetics of somatropin are similar in men and women.

Patients with Renal or Hepatic Impairment — No studies have been performed with somatropin.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
ZOMACTON has shown no potential for mutagenicity in Ames Test. Carcinogenesis and fertility studies have not been conducted with ZOMACTON.

14 CLINICAL STUDIES
14.1 Pediatric Patients with Short Stature Due to Growth Hormone Deficiency
ZOMACTON was tested in the United States and in Israel in a 2-year open-label, multi-center study in 164 pediatric patients with short stature due to GHD. The subjects ranged in age from 2.1 to 17.7 years with a mean of 10.8 years. One hundred twenty (73%) of the subjects were male and 44 (27%) were female. Two subjects were Asian, 12 were Black, 130 were Caucasian, and 20 were categorized as 'other'.

The primary efficacy of the product was assessed by calculating height velocity. Mean cumulative increases in height velocity from baseline of 6.6, 4.6, and 6.3 cm/year were attained by 24 weeks of treatment ($p < 0.01$) in Naïve Type I (serum GH < 10 ng/mL in response to at least two provocative pharmacological tests), Naïve Type II (integrated GH level < 3.5 ng/mL with or without at least one serum GH ≥ 10 ng/mL), and Non-Naïve (treated with GH up to study Day 1, or previously treated and discontinued GH treatment at least 6 months prior to study Day 1) subjects, respectively. After 12 months of treatment, the mean cumulative increases in height velocity from baseline were 5.7, 4.4 and 5.3 cm/year (p= 0.01) in Naïve Type I, Naïve Type II, and Non-Naïve subjects, respectively.

14.2 Adult Patients with Growth Hormone Deficiency
Two studies in patients with adult-onset GH deficiency (total n=98) and two studies in adult patients with childhood-onset GH deficiency (total n=67) were designed to assess the effects of replacement therapy with another somatropin product. Adult-onset patients and childhood-onset patients differed by diagnosis (organic vs. idiopathic pituitary disease), body size (average vs. small [mean height and weight]), and age (mean 44 vs. 29 years). These four studies each included a 6-month randomized, blinded, placebo-controlled phase, during which approximately half of the patients received placebo injections, while the other half received injections with another somatropin product. The 6-month, double-blind phase was followed by 12 months of open-label somatropin treatment for all patients. The dosages of this other somatropin product for all studies were identical: 1 month of treatment at 0.00625 mg/kg/day followed by 0.0125 mg/kg/day for the next 5 months. The primary efficacy measures were body composition (lean body mass and fat mass) and lipid parameters. Lean body mass was determined by bioelectrical impedance analysis (BIA), validated with potassium 40. Body fat was assessed by BIA and sum of skinfold thickness. Lipid subfractions were analyzed by standard assay methods in a central laboratory.

In patients with adult-onset GH deficiency, treatment with another somatropin product (vs. placebo) resulted in an increase in mean lean body mass (2.59 vs. -0.22 kg, p<0.001) and a decrease in body fat (-3.27 vs. 0.56 kg, p<0.001). Similar changes were seen in childhood-onset GH deficient patients. Changes in lean body mass persisted throughout the 18-month period for both the adult-onset and childhood-onset groups; the changes in fat mass persisted in the childhood-onset group. Serum concentrations of high-density lipoprotein (HDL) cholesterol which were low at baseline (mean, 30.1 mg/mL and 33.9 mg/mL in adult-onset and childhood-onset patients, respectively) had normalized by the end of 18 months of treatment with this other somatropin product (mean change of 13.7 mg/dL and 11.1 mg/dL for the adult-onset and childhood-onset groups, respectively p<0.001).

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
ZOMACTON for injection is a white, lyophilized powder available as:

NDC	ZOMACTON	Diluent	Additional Items
NDC 55566-1801-1	5 mg vial	5 mL vial bacteriostatic 0.9% sodium chloride	
NDC 55566-1901-1	10 mg vial	1 mL syringe bacteriostatic water	25G reconstitution needle
NDC 55566-1902-1	10 mg vial	1 mL syringe bacteriostatic water	vial adapter

16.2 Storage and Handling

Before Reconstitution

Refrigerate ZOMACTON vials at 36° to 46°F (2° to 8°C). Avoid freezing the accompanying diluent.

After Reconstitution

ZOMACTON 5 mg is stable for 14 days when reconstituted with bacteriostatic 0.9% sodium chloride and refrigerated at 36° to 46°F (2° to 8°C).
Do not freeze.

ZOMACTON 10 mg is stable for 28 days when reconstituted with bacteriostatic water and refrigerated at 36° to 46°F (2° to 8°C). Do not freeze.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

- Neoplasms – Advise childhood cancer survivors/caregivers that individuals treated with brain/head radiation are at increased risk of secondary neoplasms and as a precaution need to be monitored for recurrence. Advise patients/caregivers to report marked changes in behavior, onset of headaches, vision disturbances and/or changes in skin pigmentation or changes in the appearance of pre-existing nevi.
- Fluid Retention - Advise patients that fluid retention during ZOMACTON replacement therapy in adults may frequently occur. Inform patients of the clinical manifestations of fluid retention (e.g. edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/ paraesthesias) and to report to their healthcare provider any of these signs or symptoms occur during treatment with ZOMACTON.
- Pancreatitis - Advise patients/caregivers that pancreatitis may develop and to report to their healthcare provider any new onset abdominal pain.
- Hypoadrenalism - Advise patients/caregivers who have or who are at risk for pituitary hormone deficiency(s) that hypoadrenalism may develop and to report to their healthcare provider if they experience hyperpigmentation, extreme fatigue, dizziness, weakness, or weight loss.
- Hypothyroidism - Advise patients/caregivers that undiagnosed/untreated hypothyroidism may prevent an optimal response to ZOMACTON. Advise patients/caregivers they may require periodic thyroid function tests.
- Intracranial Hypertension - Advise patients/caregivers to report to their healthcare provider any visual changes, headache, and nausea and/or vomiting.
- Hypersensitivity Reactions – Advise patients/caregivers that serious systemic hypersensitivity reactions (anaphylaxis and angioedema) are possible and that prompt medical attention should be sought if an allergic reaction occurs.
- Glucose Intolerance/ Diabetes Mellitus – Advise patients/caregivers that new onset impaired glucose intolerance/diabetes mellitus or exacerbation of preexisting diabetes mellitus can occur and monitoring of blood glucose during treatment with ZOMACTON may be needed.
- Women of Reproductive Potential – Instruct patients to inform their healthcare provider if they are pregnant or planning to become pregnant as they may potentially require the use of a different formulation of ZOMACTON.

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MANUFACTURED FOR:
FERRING PHARMACEUTICALS

FERRING PHARMACEUTICALS INC.
PARSIPPANY, NJ 07054

Origin Germany

2009054868
Rev. 1/2018

Mixing ZOMACTON
- Hold the vial between your hands and gently roll it until the mixture is clear. **Do not shake the vial.** Your ZOMACTON is ready for injection.
- Sometimes the vial may need to sit a few seconds before the mixture becomes clear. **Do not** use the mixture in the vial if it remains cloudy or you see particles floating in the mixture. If air bubbles appear, let the growth hormone sit for a while until they disappear.
- Write the date you mixed the growth hormone on the vial label. The **5** mg vial must be used within **14** days. The 10mg vial must be used within **28** days.
- Store your **mixed** growth hormone and all **unopened vials** of growth hormone in the refrigerator at 36°F to 46°F (2°C to 8°C). **Do not** freeze.

Step 1: Preparing the Injection
You are now ready for your ZOMACTON injection.
- Wash your hands thoroughly with soap and water.
- Check that the vial of growth hormone you are using is clear and that the date of mixing is within **14** days if you are using ZOMACTON **5**mg or **28** days if you are using ZOMACTON **10**mg.
- Clean the top of the growth hormone vial with an alcohol swab. **Do not** touch the rubber stopper after cleaning **(See Figure O)**.

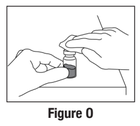
Figure O

- Remove the needle cap from the syringe and insert the needle into the center of the rubber stopper on the growth hormone vial **(See Figure P)**.

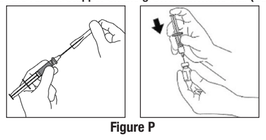
Figure P

- Gently pull back the plunger until the amount of growth hormone solution your healthcare provider has prescribed is in the syringe **(See Figure Q)**.

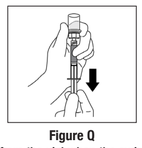
Figure Q

- Remove the needle from the vial when the syringe is correctly filled with the solution **(See Figure R)**. Recap the needle.

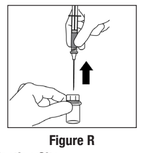
Figure R

Step 2: Choosing an Injection Site
- There are different sites you can use for your injections. These sites should be rotated **(See Figure S)**.

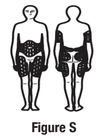
Figure S

If you notice any of the following signs, contact your healthcare provider:
- A lump, bruise or redness at the injection site that does not go away.
- Any sign of infection at the injection site (pus, redness, heat or persistent pain).
- Severe, sharp pain or ache at injection site that does not go away.
- Rash at the injection site.

Step 3: Injecting ZOMACTON
- Using a circular motion, clean the injection site with an alcohol swab, starting at the injection site and moving outward about 2 inches. Let the skin air dry.
- Check that the correct dose is in the syringe.
- Remove the needle cap. Hold the syringe like a pencil in 1 hand.
- With your free hand, pinch the skin around the site with the thumb and forefinger of the other hand **(See Figure T)**. Quickly insert the needle into the skin at a 45° - 90° angle with a quick, dart-like motion.

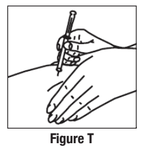
Figure T

- Holding the syringe in place, pull back a little on the plunger and check to see if any blood flows into the syringe **(See Figure U)**. If you **see blood in the syringe**, it means that you have entered a blood vessel. **Do not** inject ZOMACTON. Withdraw the needle. Throw away the syringe and needle in a puncture-resistant container. Do not use the same syringe or any of the other supplies that you used for this injection. Repeat the steps to prepare a new syringe for injection. Choose and clean a new injection site.

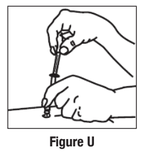
Figure U

- If no blood appears in the syringe, slowly push down plunger all the way until the syringe is completely empty **(See Figure V)**.

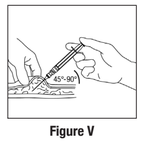

Figure V

- Quickly remove the needle from the skin and apply pressure to the injection site with a dry sterile gauze pad or cotton ball. A drop of blood may appear. Apply a small bandage if needed. Throw away the needle and syringe in your puncture-resistant disposal container.
- Do not share your syringes, needles, or vials with anyone else. You may give them or get an infection from them.

Step 4: Disposing of used syringes, needles, and vials
- To prevent needle-stick injury and spread of infection, do not try to re-cap the needle.
- Place used needles, syringes, and vials in a closeable, puncture-resistant container. You may use a sharps container (such as a red biohazard container), hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). Do not use glass or clear plastic containers. Ask your healthcare provider for instructions on the right way to throw away (dispose of) the container. There may be state and local laws about how you should throw away used needles and syringes.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal
- **Do not throw used needles, syringes, or vials in your household trash or recycle.**
- Keep the disposal container, needles, syringes, and vials of ZOMACTON out of reach of children.

This Instructions for Use has been approved by the Food and Drug Administration.

MANUFACTURED FOR:
FERRING PHARMACEUTICALS

FERRING PHARMACEUTICALS INC.
PARSIPPANY, NJ 07054

Origin Germany

2009054868
Rev. 1/2018

FERRING PHARMACEUTICALS

ZOMACTON®

(somatropin) for Injection
5mg and 10mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOMACTON® safely and effectively. See full prescribing information for ZOMACTON.

ZOMACTON® (somatropin) for injection, for subcutaneous use
Initial U.S. Approval: 1995

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	1/2018
Dosage and Administration (2)	1/2018
Contraindications (4)	1/2018
Warnings and Precautions (5)	1/2018

----------INDICATIONS AND USAGE----------

ZOMACTON is a recombinant human growth hormone (GH) indicated for:
- Treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous GH (1.1)
- Replacement of endogenous GH in adults with GH deficiency (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Administer by subcutaneous injection to the back of upper arm, abdomen, buttock, or thigh with regular rotation of injection sites (2.1)
- *Pediatric dosage:*
  - Divide the calculated weekly dosage into equal doses given either 3, 6, or 7 days per week (2.2)
  - The recommended weekly dose is 0.18 mg/kg/week to 0.3 mg/kg/week (2.2)
- *Adult dosage:* Either of the following two dosing regimens may be used:
  - *Non-weight based dosing:* Initiate with a dose of approximately 0.2 mg/day (range, 0.15 mg/day-0.3 mg/day) and increase the dose every 1-2 months by increments of approximately 0.1 mg/day-0.2 mg/day, according to individual patient requirements (2.3)
  - *Weight-based dosing (Not recommended for obese patients):* Initiate at 0.006 mg/kg daily and increase the dose according to individual patient requirements to a maximum of 0.0125 mg/kg daily (2.3)
- See Full Prescribing Information for reconstitution instructions (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

ZOMACTON for injection is available as (3):
- 5 mg vial with 5 mL vial of bacteriostatic 0.9% sodium chloride (preserved with benzyl alcohol)
- 10 mg vial with syringe of 1 mL of bacteriostatic water (preserved with 0.33% metacresol), with a 25G reconstitution needle
- 10 mg vial with syringe of 1 mL of bacteriostatic water (preserved with 0.33% metacresol), with a vial adapter

----------CONTRAINDICATIONS----------
- Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or acute respiratory failure (4,5.1)
- Pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment (4, 5.2)
- Active malignancy (4)
- Hypersensitivity to ZOMACTON, its excipients, or diluents (4)
- Active proliferative or severe non-proliferative diabetic retinopathy (4)
- Pediatric patients with closed epiphyses (4)

----------WARNINGS AND PRECAUTIONS----------
- *Increased Risk of Neoplasm:* Occurred in childhood cancer survivors. Monitor patients with preexisting tumors for progression or recurrence. (5.3)
- *Glucose Intolerance and Diabetes Mellitus:* ZOMACTON may decrease insulin sensitivity, particularly at higher doses. Monitor glucose levels periodically in all patients receiving ZOMACTON, especially in patients with existing diabetes mellitus or at risk for development. (5.4)
- *Intracranial Hypertension (IH):* Has been reported usually within 8 weeks of initiation. Perform fundoscopic examinations prior to initiation and periodically thereafter. If papilledema occurs, stop treatment. (5.5)
- *Hypersensitivity:* Serious hypersensitivity reactions may occur. In the event of an allergic reaction, seek prompt medical attention. (5.6)
- *Fluid Retention:* May occur in adults and may be dose dependent. (5.7)
- *Hypoadrenalism:* Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism. (5.8)
- *Hypothyroidism:* Monitor thyroid function periodically as hypothyroidism may occur or worsen after initiation of somatropin. (5.9)
- *Slipped Capital Femoral Epiphysis in Pediatric Patients:* May occur; evaluate patients with onset of a limp or hip/knee pain. (5.10)
- *Progression of Preexisting Scoliosis in Pediatric Patients:* Monitor patients with scoliosis for progression. (5.11)
- *Pancreatitis:* Has been reported; consider pancreatitis in patients with abdominal pain, especially pediatric patients. (5.12)
- *Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative:* Serious and fatal adverse reactions can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including the diluent for ZOMACTON 5 mg. If administering ZOMACTON 5 mg to infants, reconstitute with normal saline. (5.13)

----------ADVERSE REACTIONS----------

Most common adverse reactions (10% or greater incidence) in adult and pediatric patients include: upper respiratory infection, fever, pharyngitis, headache, otitis media, edema, arthralgia, paresthesia, myalgia, pain, rhinitis, peripheral edema, back pain, flu syndrome, and AST increased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ferring Pharmaceuticals Inc. at 1-888-337-7464 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Glucocorticoids:* Patients treated with glucocorticoid for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of ZOMACTON (7)
- *Pharmacologic Glucocorticoid Therapy and Supraphysiologic Glucocorticoid Treatment:* Adjust glucocorticoid replacement dosing in pediatric patients receiving glucocorticoid treatment to avoid both hypoadrenalism and an inhibitory effect on growth. (7)
- *Cytochrome P450-Metabolized Drugs:* ZOMACTON may alter the clearance. Monitor carefully if used with ZOMACTON (7)
- *Oral Estrogen:* Larger doses of ZOMACTON may be required (7)
- *Insulin and/or Other Hypoglycemic Agents:* Dose adjustment of insulin or hypoglycemic agent may be required (5.4, 7)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy and Lactation:* If ZOMACTON 5 mg is needed, reconstitute with normal saline, or use the ZOMACTON 10 mg benzyl alcohol-free formulation. (8.1, 8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2018

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pediatric Patients
ZOMACTON is indicated for the treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone (GH).

1.2 Adult Patients
ZOMACTON is indicated for the replacement of endogenous GH in adults with GH deficiency.

2 DOSAGE AND ADMINISTRATION

2.1 Administration and Use Instructions
- Therapy with ZOMACTON should be supervised by a physician who is experienced in the diagnosis and management of patients with the conditions for which ZOMACTON is indicated *[see Indications and Usage (1)]*.
- Fundoscopic examination should be performed routinely before initiating treatment with ZOMACTON to exclude preexisting papilledema, and periodically thereafter *[see Warnings and Precautions (5.5)]*.
- Administer ZOMACTON by subcutaneous injection to the back of the upper arm, abdomen, buttock, or thigh with regular rotation of injection sites to avoid lipoatrophy.
- ZOMACTON 5 mg and 10 mg can be administered using a standard sterile disposable syringe or a ZOMA-Jet® Needle Free Delivery Device, using the respective device (i.e., 5 mg or 10 mg ZOMA-Jet® Needle Free Delivery Device). For proper use, please refer to the Instructions for Use provided with the administration device. If using a syringe, the volume of the syringe should be small enough so that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

2.2 Pediatric Dosage
- Individualize dosage for each patient based on the growth response.
- Divide the calculated weekly ZOMACTON dosage into equal doses given either 3, 6, or 7 days per week.
- The recommended weekly dose in milligrams (mg) per kilogram (kg) of body weight for pediatric patients is 0.18 mg/kg/week to 0.3 mg/kg/week (0.026 mg/kg/day to 0.043 mg/kg/day).
- Assess compliance and evaluate other causes of poor growth such as hypothyroidism, under-nutrition, advanced bone age and antibodies to recombinant human GH if patients experience failure to increase height velocity, particularly during the first year of treatment.
- Discontinue ZOMACTON for stimulation of linear growth once epiphyseal fusion has occurred *[see Contraindications (4)]*.

2.3 Adult Dosage
- Patients who were treated with somatropin for GH deficiency in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin for GH deficient adults.
- Consider using a lower starting dose and smaller dose increment increases for geriatric patients as they may be at increased risk for adverse reactions with ZOMACTON than younger individuals *[see Use in Specific Populations (8.5)]*.
- Estrogen-replete women and patients receiving oral estrogen may require higher doses *[see Drug Interactions (7.1)]*.
- Administer the prescribed dose daily
- Either of two ZOMACTON dosing regimens may be used:
  - Non-weight based
    - Initiate ZOMACTON with a dose of approximately 0.2 mg/day (range, 0.15 mg/day to 0.3 mg/day) and increase the dose every 1-2 months by increments of approximately 0.1 mg/day to 0.2 mg/day, according to individual patient requirements based on the clinical response and serum insulin-like growth factor 1 (IGF-1) concentrations.
    - Decrease the dose as necessary on the basis of adverse reactions and/or serum IGF-1 concentrations above the age- and gender-specific normal range.
    - Maintenance dosages will vary considerably from person to person, and between male and female patients.
  - Weight-based
    - Initiate ZOMACTON at 0.006 mg/kg daily and increase the dose according to individual patient requirements to a maximum of 0.0125 mg/kg daily.
    - Use the patient's clinical response, adverse reactions, and determination of age- and gender-adjusted serum IGF-1 concentrations as guidance in dose titration.
    - Not recommended for obese patients as they are more likely to experience adverse reactions with this regimen.

2.4 Reconstitution
- Reconstitute ZOMACTON 5 mg with 1 mL to 5 mL of bacteriostatic 0.9% sodium chloride diluent. Do not use diluent if the patient has a known hypersensitivity to benzyl alcohol *[see Contraindications (4)]* or in neonates *[see Warnings and Precautions (5.13)]*, or pregnant or lactating women *[see Use in Specific Populations (8.1,8.2)]* instead use normal saline, use only one dose per vial, and discard the remaining dose of the reconstituted product after use.
- Reconstitute ZOMACTON 10 mg with 1 mL syringe of bacteriostatic water for injection diluent. Do not use diluent if the patient has a known hypersensitivity to metacresol *[see Contraindications (4)]*.
- Aim the stream of diluent against the side of the vial to prevent foaming and gently swirl the vial with a rotary motion until the contents are completely dissolved and the solution is clear. Do not shake the vial since shaking or vigorous mixing will cause the solution to be cloudy.
- Inspect visually for particulate matter and discoloration. If the resulting solution is cloudy or contains particulate matter do not use.
- Occasionally, after refrigeration, some cloudiness may occur. Allow the product to warm to room temperature. If cloudiness persists or particulate matter is noted do not use.

3 DOSAGE FORMS AND STRENGTHS
ZOMACTON for injection is a white, lyophilized powder available as:
- 5 mg vial with a 5 mL vial of bacteriostatic 0.9% sodium chloride [preserved with benzyl alcohol]
- 10 mg vial with a syringe of 1 mL of bacteriostatic water [preserved with metacresol] with a 25G reconstitution needle
- 10 mg vial with a syringe of 1 mL of bacteriostatic water [preserved with metacresol] with a vial adapter

4 CONTRAINDICATIONS
ZOMACTON is contraindicated in patients with:
- Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin *[see Warnings and Precautions (5.1)]*.
- Pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to the risk of death *[see Warnings and Precautions (5.2)]*.
- Active malignancy due to an increased risk of second neoplasm *[see Warnings and Precautions (5.3)]*.
- Hypersensitivity to ZOMACTON, any of its excipients, or its accompanying diluents. Systemic hypersensitivity reactions have been reported with postmarketing use of somatropin products *[see Dosage and Administrations (2.4), Warnings and Precautions (5.6)]*.
- Active proliferative or severe non-proliferative diabetic retinopathy.
- Pediatric patients with closed epiphyses.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Patients with Acute Critical Illness
Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic doses of somatropin [*see Contraindications (4)]*. Two placebo-controlled clinical trials in non-GH deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (42% vs. 19%) among somatropin-treated patients (doses 5.3 mg/day-8 mg/day) compared to those receiving placebo. The safety of continuing ZOMACTON treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. ZOMACTON is not indicated for the treatment of non-GH deficient adults.

5.2 Fatalities in Pediatric 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 greater risk than females. Patients with Prader-Willi syndrome 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 new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome 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 treated aggressively *[see Contraindications (4)]*. ZOMACTON is not indicated for the treatment of pediatric patients who have growth failure due to Prader-Willi syndrome.

5.3 Increased risk of Neoplasms
In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent GH deficiency and were treated with somatropin, an increased risk of a second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence *[see Contraindications (4)]*. Monitor all patients receiving ZOMACTON who have a history of GH deficiency secondary to an intracranial neoplasm for progression or recurrence of the tumor.

Because pediatric patients with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting ZOMACTON in these patients. If ZOMACTON is initiated, these patients should be carefully monitored for development of neoplasms. ZOMACTON is not indicated for the treatment of non-GH deficient pediatric patients with short stature.

Monitor patients receiving ZOMACTON carefully for increased growth, or potential malignant changes, of preexisting nevi. Advise patients/caregivers to report marked changes in behavior, onset of headaches, vision disturbances and/or changes in skin pigmentation or changes in the appearance of pre-existing nevi.

5.4 Glucose Intolerance and Diabetes Mellitus
Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes mellitus has been reported in patients taking somatropin. Previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked. Monitor glucose levels periodically in all patients receiving ZOMACTON, especially in those with risk factors for diabetes mellitus, such as obesity or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely. The doses of antidiabetic agents may require adjustment when ZOMACTON is initiated.

5.5 Intracranial Hypertension
Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin. In all reported cases, IH-associated signs and symptoms resolved rapidly after cessation of therapy or a reduction of the somatropin dose. Fundoscopic examination should be performed routinely before initiating treatment with ZOMACTON to exclude preexisting papilledema, and periodically thereafter. If papilledema is observed by fundoscopy, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with ZOMACTON can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome may be at increased risk for the development of IH. ZOMACTON is not indicated for the treatment of pediatric patients who have growth failure due to Turner syndrome.

5.6 Severe Hypersensitivity
Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing 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 *[see Contraindications (4)]*.

5.7 Fluid Retention
Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention (e.g. edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias) are usually transient and dose dependent.

5.8 Hypoadrenalism
Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of ZOMACTON. Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism *[see Drug Interactions (7)]*.

5.9 Hypothyroidism
Undiagnosed or untreated hypothyroidism may prevent an optimal response to ZOMACTON, in particular, the growth response in pediatric patients. In patients with GH deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients should have periodic thyroid function tests performed, and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

5.10 Slipped Capital Femoral Epiphysis in Pediatric Patients
Slipped capital femoral epiphysis may occur more frequently in patients undergoing rapid growth. Evaluate pediatric patients with the onset of a limp or complaints of hip or knee pain.

5.11 Progression of Preexisting Scoliosis in Pediatric Patients
Somatropin increases the growth rate and progression of existing scoliosis can occur in patients who experience rapid growth. Somatropin has not been shown to increase the occurrence of scoliosis. Monitor patients with a history of scoliosis for progression of scoliosis.

5.12 Pancreatitis
Cases of pancreatitis have been reported in pediatric patients and adults receiving somatropin. The risk may be greater in pediatric patients compared with adults. Pancreatitis should be considered in patients who develop abdominal pain.

5.13 Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative
Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including the bacteriostatic 0.9% sodium chloride diluent provided with ZOMACTON 5 mg. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

When administering ZOMACTON 5 mg to infants, reconstitute with normal saline, not the diluent provided. Only one dose should be used per vial and the reconstituted product should be discarded after use *[see Use in Specific Populations (8.4)]*.

5.14 Lipoatrophy
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 *[see Dosage and Administration (2.2)]*.

5.15 Laboratory Tests
Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone and IGF-1 may increase after ZOMACTON treatment

6 ADVERSE REACTIONS
The following important adverse reactions are also described elsewhere in the labeling:
- Increased mortality in patients with acute critical illness *[see Warnings and Precautions (5.1)]*
- Fatalities in pediatric patients with Prader-Willi syndrome *[see Warnings and Precautions (5.2)]*
- Neoplasms *[see Warnings and Precautions (5.3)]*
- Glucose intolerance and diabetes mellitus *[see Warnings and Precautions (5.4)]*
- Intracranial hypertension *[see Warnings and Precautions (5.5)]*
- Severe hypersensitivity *[see Warnings and Precautions (5.6)]*
- Fluid retention *[see Warnings and Precautions (5.7)]*
- Hypoadrenalism *[see Warnings and Precautions (5.8)]*
- Hypothyroidism *[see Warnings and Precautions (5.9)]*
- Slipped capital femoral epiphysis in pediatric patients *[see Warnings and Precautions (5.10)]*
- Progression of preexisting scoliosis in pediatric patients *[see Warnings and Precautions (5.11)]*
- Pancreatitis *[see Warnings and Precautions (5.12)]*
- Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative *[see Warnings and Precautions (5.13)]*
- Lipoatrophy *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a different approved somatropin formulation, and may not reflect the adverse reaction rates observed in practice.

Pediatric Patients
ZOMACTON was evaluated in 164 pediatric patients with short stature due to GHD in an open-label, multi-center study conducted in the United States and Israel. The protocol was designed to study the safety and efficacy of somatropin through 24 weeks and later extended for up to 4 years. The subjects ranged in age from 2.1 to 17.7 years with a mean of 10.8 years. One hundred twenty (73%) of the subjects were male and 44 (27%) were female. Two subjects were Asian, 12 were Black, 130 were Caucasian, and 20 were categorized as 'other'.

Table 1: Adverse Reactions ≥ 5% in Pediatric Patients with Short Stature Due to GHD Treated with ZOMACTON through 24 Weeks

Adverse Reaction	24 Week Exposure to ZOMACTON (n=164)
Upper respiratory infection	32%
Fever	16%
Pharyngitis	12%
Headache	11%
Otitis Media	10%
Increased cough	9%
Abdominal pain	7%
Anemia	6%
Maculopapular rash	6%
Diarrhea	5%
Pain	5%
Rhinitis	5%

All pediatric patients were carefully observed for signs or laboratory abnormalities of hypothyroidism. Fifteen patients had T4 values which occasionally fell below the central laboratory's lower limit of normal; T4 levels rose to normal when tested during the next visit for all patients except one who continued to be monitored. Six of the 15 patients received thyroxine therapy before and throughout the study period, and thyroxine dose adjustments were made during the study in 3/6 subjects.

In studies with GH deficient pediatric patients, injection site pain was reported infrequently. A mild and transient edema, which appeared in 2.5% of patients, was observed early during the course of treatment.

Adult Patients
Adult-Onset GH Deficiency
In the first 6 months of controlled blinded trials during which patients received either another somatropin product or placebo, patients who received this other somatropin product experienced a statistically significant increase in edema (another somatropin product 17% vs. placebo 4%, p=0.043) and peripheral edema (12% vs. 0%, respectively, p=0.017). Edema, muscle pain, joint pain, and joint disorder were reported early in therapy and tended to be transient or responsive to dosage titration.

Two of 113 patients developed carpal tunnel syndrome after beginning maintenance therapy without a low dose (0.00625 mg/kg/day) lead-in phase. Symptoms abated in these patients after dosage reduction.

ZOMACTON®
(zoh-MACK-ton)
(somatropin)
for Injection

Read the Instructions for Use that come with your ZOMACTON® before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment. Before you use ZOMACTON for the first time, make sure your healthcare provider shows you the right way to use it.

Supplies needed for your ZOMACTON Injection
- **ZOMACTON 5mg (See Figure A)** containing:
  - 1 vial of ZOMACTON 5mg growth hormone in a powder
  - 1 vial of liquid (diluent) containing Bacteriostatic 0.9% Sodium Chloride Injection, USP (5mL). This is used to mix your ZOMACTON 5mg.

Figure A

or
- **ZOMACTON 10mg (See Figure B) containing:**
  - 1 vial of ZOMACTON 10mg growth hormone in a powder
  - 1 syringe of liquid (diluent) containing Bacteriostatic Water for Injection with 0.33% Metacresol as a preservative (1mL). This is used to mix your ZOMACTON 10mg.
  - 25 gauge mixing needle

Figure B

The following additional supplies **(See Figure C)** will be needed:
- Syringe and needle for injection. Your healthcare provider will tell you the size of the syringe and needle to use.
- Alcohol swab
- Puncture-resistant container **(See Step 4: Disposing of used syringes, needles, and vials)**

Figure C

Preparing for Your ZOMACTON Injection
- Place the supplies you will need on a clean, flat surface in a well-lit area.
- Wash your hands thoroughly with soap and water.

Important: The liquids are different for the 5mg and 10mg vials.
- **Do not** use the 5mg liquid with the 10mg ZOMACTON.
- **Do not** use the 10mg liquid with the 5mg ZOMACTON.

Preparing ZOMACTON 5mg Liquid for Injection:
- Remove the hard plastic cap from the top of the liquid vial by gently pushing up on the edge of the cap **(See Figure D)**. **Do not** remove the rubber stopper.

Figure D

- Use an alcohol swab to wipe off the top of the liquid vial **(See Figure E)**. After cleaning, **do not** touch the rubber stopper.

Figure E

- Remove the needle cap from the syringe while making sure you **do not** touch the needle **(See Figure F)**. **Do not** throw away the needle cap.

Figure F

- Hold the barrel of the syringe with **1** hand and pull back on the plunger with the other hand until you have drawn up the amount of air that is the same as the amount of liquid your healthcare provider has prescribed **(See Figure G)**.

Figure G

- Insert the needle into the liquid vial through the center of the clean rubber stopper. Push down on the plunger until all the air is released into the vial **(See Figure H)**.

Figure H

- Hold the vial with **1** hand and carefully turn the vial upside down making sure the syringe needle stays in the vial. **The tip of the needle should be below the surface of the liquid.**
- With your other hand, gently pull back the plunger until the amount of liquid your healthcare provider prescribed is in the syringe **(See Figure I)**.

Figure I

- When the syringe is correctly filled with the liquid, remove the syringe and needle from the vial and recap the needle.

Preparing ZOMACTON 10mg Liquid for Injection:
- Remove the syringe tip cap from the top of the pre-filled liquid syringe and attach the **25G** mixing needle that comes with your ZOMACTON **(See Figure J)**.

Figure J

Diluting Your ZOMACTON
- **Only** use the liquid that comes with the 5mg ZOMACTON to mix the 5mg growth hormone. **Only** use the liquid that comes with the 10mg ZOMACTON to mix the 10mg growth hormone.
- Remove the hard plastic cap of the growth hormone vial **(See Figure K)**.

Figure K

- Clean the top of the growth hormone vial with an alcohol swab **(See Figure L)**.

Figure L

- Remove the needle cap from the syringe filled with liquid and insert the needle into the center of the rubber stopper on the growth hormone vial **(See Figure M)**.

Figure M

- Point the needle toward the side of the vial and slowly push the plunger so that the liquid squirts onto the side of the vial and not directly onto the powder.
- When all the liquid is in the growth hormone vial, remove the needle from the vial **(See Figure N)**.

Figure N

- Recap the needle and throw away the syringe.