

1. NAME OF THE MEDICINAL PRODUCT

ZOMACTON 10 mg/ml, powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Somatropin*10 mg
(10 mg/ml after reconstitution for one vial)

* Produced in *Escherichia coli* cells using recombinant DNA technology

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Zomacton is a white to off-white lyophilised powder. The solvent in syringe is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zomacton is indicated for:

- the long-term treatment of children who have growth failure due to inadequate secretion of growth hormone
- the long-term treatment of growth retardation due to Turner's Syndrome confirmed by chromosome analysis.

4.2 Posology and method of administration

Zomacton therapy should be used only under the supervision of a qualified physician experienced in the management of patients with growth hormone deficiency.

The dosage of administration of Zomacton should be individualised for each patient.

The duration of treatment, usually a period of several years will depend on maximum achievable therapeutic benefit.

The subcutaneous administration of growth hormone may lead to loss or increase of adipose tissue at the injection site. Therefore, injection sites should be alternated.

Growth Hormone Deficiency

Generally a dose of 0.17 – 0.23 mg/kg bodyweight (approximating to 4.9 mg/m² – 6.9 mg/m² body surface area) per week divided into 6 - 7 s.c. injections is recommended (corresponding to a daily injection of 0.02 – 0.03 mg/kg bodyweight or 0.7 – 1.0 mg/m² body surface area). The total weekly dose of 0.27 mg/kg or 8 mg/m² body surface area should not be exceeded (corresponding to daily injections of up to about 0.04 mg/kg).

Turner's Syndrome

Generally a dose of 0.33 mg/kg/bodyweight (approximating to 9.86 mg/m²/body surface area) per week divided into 6 - 7 s.c. injections are recommended (corresponding to daily injection of 0.05 mg/kg/bodyweight or 1.40-1.63 mg/m²/body surface area).

Instructions for preparation, see section 6.6.

Administration

The required dose of ZOMACTON 10 mg/ml is administered with a ZomaJet 10 needle-free device or with an ordinary syringe.

Specific instructions for the use of the ZomaJet 10 device are given in a booklet supplied with the device.

4.3 Contraindications

Hypersensitivity to somatotropin or to any of the excipients listed in section 6.1.

Somatropin must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting GH therapy. Treatment should be discontinued if there is evidence of tumour growth.

Somatropin should not be used for growth promotion in children with closed epiphyses. Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with somatotropin.

In children with chronic renal disease, treatment with somatotropin should be discontinued at renal transplantation.

4.4 Special warnings and precautions for use

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

Very rare cases of myositis have been observed and may be due to the metacresol used as preservative. In the case of myalgia or disproportionate pain at the injection site, myositis

should be considered and, if confirmed, a Zomacton presentation without metacresol should be used.

Patients with Prader-Willi syndrome

Zomacton is not indicated for the long term treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome, unless they also have a diagnosis of GH deficiency. There have been reports of sleep apnoea and sudden death after initiating therapy with growth hormone in paediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea or unidentified respiratory infection.

Intra-cranial hypertension

Rare cases of benign intra-cranial hypertension have been reported. In the event of severe or recurring headache, visual problems, and nausea/vomiting, a funduscopy for papilla edema is recommended. If papilla edema is confirmed, diagnosis of benign intra-cranial hypertension should be considered and if appropriate growth hormone treatment should be discontinued (see also section 4.8). At present, there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Leukaemia

Leukaemia has been reported in a small number of growth hormone deficient patients treated with somatropin as well as in untreated patients. However, there is no evidence that leukaemia incidence is increased in growth hormone recipients without predisposition factors.

Development of antibodies

As with all somatropin containing products, a small percentage of patients may develop antibodies to somatropin. The binding capacity of these antibodies is low and there is no effect on growth rate. Testing for antibodies to somatropin should be carried out in any patient who fails to respond to therapy.

Hypothyroidism

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may, as such, unmask insipiens hypothyroidism. Monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism, standard replacement therapy must be closely monitored when somatropin therapy is administered.

Patients with diabetes mellitus

Because somatropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin containing product therapy is initiated. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy. Zomacton should also be used with caution in patients with a family history predisposing for the disease.

Patients with intra-cranial lesions

In patients with growth hormone deficiency secondary to an intra-cranial lesion, frequent monitoring for progression or recurrence of the underlying disease process is advised. In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumours, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms

Discontinue Zomacton therapy if progression or recurrence of the lesion occurs. In patients with previous malignant diseases special attention should be given to signs and symptoms of relapse.

Scoliosis

Scoliosis may progress in any child during rapid growth. Signs of scoliosis should be monitored during somatropin treatment.

Patients with endocrine disorders

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders. A patient treated with Zomacton who develops a limp or complains of hip or knee pain should be evaluated by a physician.

Patients suffering complications following surgery

The effects of treatment with growth hormone on recovery were studied in two placebo controlled trials involving 522 critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, or acute respiratory failure.

Mortality was higher (42 % vs. 19 %) among patients treated with growth hormones (doses 5.3 to 8 mg/day) compared to those receiving placebo. Based on this information, such patients should not be treated with growth hormones. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved.

Experience of local tolerability to administration of ZOMACTON 10 mg/ml with ZomaJet 10 needle-free device has been studied before marketing authorisation in a 12 week study including only Caucasian children.

Although rare, pancreatitis should be considered in somatropin-treated patients, especially children who develop abdominal pain.

Introduction of somatropin treatment may result in inhibition of 11 β HSD-1 and reduced serum cortisol concentrations. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement therapy for previously

diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of somatropin treatment (see section 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of somatropin containing products. Patients with ACTH deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth hormone.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4).

High doses of androgens, oestrogens, or anabolic steroids can accelerate bone maturation and may, therefore, diminish gain in final height.

Because somatropin can induce a state of insulin resistance, insulin dose may have to be adjusted in diabetic patients receiving concomitant Zomacton.

Data from an interaction study performed in GH deficient adults suggests that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporin) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

4.6 Fertility, pregnancy and lactation

For Zomacton, no clinical data on exposed pregnancies are available. There is no data from the use of Zomacton during pregnancy in animals. (See section Preclinical safety data 5.3) Therefore, Zomacton is not recommended during pregnancy and in woman of childbearing potential not using contraception.

There have been no clinical studies conducted with somatropin containing products in breast-feeding women. It is not known whether somatropin is excreted in human milk. Therefore caution should be exercised when somatropin containing products are administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

Somatropin containing products have no influence on the ability to drive and use machines.

4.8 Undesirable effects

The subcutaneous administration of growth hormone may lead to loss or increase of adipose tissue as well as punctual haemorrhage and bruising at the injection site.

System Organ Class	Very Common (≥ 1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Very rare (<1/10,000)
Blood and lymphatic system disorders			anaemia		
Cardiac disorders			tachycardia, (adult)hypertension	(children)hypertension	
Ear and labyrinth disorders			vertigo		
Endocrine disorders		hypothyroidism			
Eye disorders			papilloedema, diplopia		
Gastrointestinal disorders			vomiting, abdominal pain, flatulence, nausea	diarrhoea	
General disorders and administration site conditions	(adults)oedema, (adults) peripheral oedema	(children)oedema, (children) peripheral oedema, injection site reactions, asthenia	weakness, injection site atrophy, injection site haemorrhage, injection site mass, hypertrophy		
Immune system disorders		antibody building			
Investigations				renal function test abnormal	
Metabolism and nutrition disorders	(adult)mild hyperglycaemia	(children)glucose tolerance impaired	hypoglycaemia, hyperphosphatemia	diabetes mellitus type II	
Musculoskeletal and connective tissue disorders	(adults)arthralgia; (adults)myalgia	(children)arthralgia; (children)myalgia (Adults) Stiffness in the extremities	muscle atrophy, bone pain, carpal tunnel syndrome (Children) Stiffness in the extremities		
Neoplasms benign, malignant and unspecified			neoplasm malignant, neoplasm		(children) leukaemia
Nervous system disorders	(adult)headache, (adult)paresthesia	headache, hypertonia, (adult)insomnia	somnolence, nystagmus	neuropathy, intracranial pressure increased, (children) insomnia, (children) paresthesia	
Psychiatric disorders			personality disorders		
Renal and urinary disorders			urinary incontinence, haematuria, polyuria, urine		

			frequency/pollakiuria , urine abnormality		
Reproductive system and breast disorders			genital discharge, (adult)gynecomastia		(children) Gynecomastia
Skin and subcutaneous tissue disorders			lipodystrophy, skin atrophy, dermatitis exfoliative, urticaria, hirsutism, skin hypertrophy		

Pancreatitis has been reported post-marketing during GH therapy (frequency unknown).

Antibodies anti-somatropin: the protein somatropin may give rise to the formation of antibodies. Depending on the concerned product, these antibodies have been identified in a definite percentage of the treated population. Their binding capacity and their titres are generally low with no clinical consequence. However, testing for antibodies to somatropin should be performed in case of absence of response to somatropin therapy.

Leukaemia: cases of leukaemia (very rare) have been reported in children with a GH deficiency, some of them being treated with somatropin and included in the post-marketing experience. However, there is no evidence of an increased risk of leukaemia without predisposition factors.

Slipped capital femoral epiphysis and Legg-Calve-Perthes disease have been reported in children treated with GH. Slipped capital femoral epiphysis occurs more frequently in case of endocrine disorders and Legg-Calve-Perthes is more frequent in case of short stature. But, it is unknown if these 2 pathologies are more frequent or not while treated with somatropin. A discomfort, a pain in the hip and/or the knee must evocate their diagnosis.

Other adverse drug reactions may be considered as class effect, as the hyperglycaemia due to the decrease of insulin-sensitivity, the decreased of free thyroxin level and the possible development of a benign intra-cranial hypertension.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The recommended dose of Zomacton should not be exceeded.

Although there have been no reports of overdose with Zomacton, acute overdose may result in an initial hypoglycaemia followed by a subsequent hyperglycaemia.

The effects of long-term, repeated use of Zomacton in doses exceeding those recommended, are unknown. However, it is possible that such use might produce signs and symptoms consistent with the known effects of excess human growth hormone (e.g. acromegaly).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatropin and somatropin agonists

ATC code: H 01 AC 01

Pharmacodynamic properties:

Identical to pituitary-derived human growth hormone (pit-hGH) in amino acid sequence, chain length (191 amino acids) and pharmacokinetic profile. Zomacton can be expected to produce the same pharmacological effects as the endogenous hormone.

Skeletal system:

Growth hormone produces a generally proportional growth of the skeletal bone in man. Increased linear growth in children with confirmed deficiency of pit-hGH has been demonstrated after exogenous administration of Zomacton. The measurable increase in height after administration of Zomacton results from an effect on the epiphyseal plates of long bones. In children who lack adequate amounts of pit-hGH, Zomacton produces increased growth rates and increased IGF-1 (Insulin-like Growth Factor/Somatomedin-C) concentrations that are similar to those seen after therapy with pit- hGH. Elevations in mean serum alkaline phosphatase concentrations are also involved.

Other organs and tissues:

An increase in size, proportional to total increase in body weight, occurs in other tissues in response to growth hormone, as well. Changes include: increased growth of connective tissues, skin and appendages; enlargement of skeletal muscle with increase in number and size of cells; growth of the thymus; liver enlargement with increased cellular proliferation; and a slight enlargement of the gonads, adrenals, and thyroid. Disproportionate growth of the skin and flat bones, and accelerated sexual maturation have not been reported in association with the growth hormone replacement therapy.

Protein, carbohydrate and lipid metabolism:

Growth hormone exerts a nitrogen-retaining effect and increases the transport of amino acids into tissue. Both processes augment the synthesis of protein. Carbohydrate use and lipogenesis are depressed by growth hormone. With large doses

or in the absence of insulin, growth hormone acts as a diabetogenic agent, producing effects seen typically during fasting (i.e. intolerance to carbohydrate, inhibition of lipogenesis, mobilisation of fat and ketosis).

Mineral metabolism:

Conservation of sodium, potassium, and phosphorous occurs after treatment with growth hormone. Increased calcium loss by the kidney is offset by increased absorption in the gut. Serum calcium concentrations are not significantly altered in patients treated with Zomacton or with pit-hGH. Increased serum concentrations of inorganic phosphates have been shown to occur both after Zomacton and pit-hGH. Accumulation of these minerals signals an increased demand during tissue synthesis.

5.2 Pharmacokinetic properties

Twenty-four (24) healthy adult subjects received 1.67 mg somatropin either by conventional s.c. injection or by ZomaJet 10 needle free device. Peak plasma levels of around 20 ng/ml were observed 3.5 to 4 hours after administration of the medicinal product.

A terminal half-life 2.6 hours was observed when the compound was administered with ZomaJet 10 needle-free device which is likely to be due to a rate limiting absorption process.

Data from other somatropin containing products suggest that the bioavailability subcutaneously administered somatropin is approximately 80% in healthy adults and that both liver and kidney have been shown to be important protein catabolism organs eliminating the compound.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity and genotoxicity.

Genetically engineered somatropin is identical to endogenous human pituitary growth hormone. It has the same biological properties and it is usually administered in physiological doses. Therefore, studies on safety pharmacology, toxicity to reproduction and carcinogenicity have not been conducted as no such effects are anticipated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Mannitol

Disodium phosphate dodecahydrate

Sodium dihydrogen phosphate dihydrate

Solvent

Metacresol

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After reconstitution, the solution must be stored for a maximum of 28 days in a refrigerator at 2°C - 8°C.

After reconstitution, store vials in an upright position.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C); keep in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Zomacton is supplied in various packs subject to national approvals:

a) Sets for use for needle injection:

Powder: Vial (type I glass) with closure (rubber, halobutyl polymer) in combination with an aluminium seal and "Flip-off" cap (plastic).

Solvent: Syringe (type I glass) with tip cap (rubber, halobutyl polymer), plunger stopper (rubber, halobutyl polymer) and a solvent transfer connector (polycarbonate).

Packs: 1, 3 and 5

b) Sets for use with the needle free device ZomaJet 10:

Powder: Vial (type I glass) with closure (rubber, halobutyl polymer) in combination with an aluminium seal and "Flip-off" cap (plastic).

Solvent: Syringe (type I glass) with tip cap (rubber, halobutyl polymer), plunger stopper (rubber, halobutyl polymer) and vial adaptor (polycarbonate and silicone rubber).

Packs: 1, 3 and 5

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitution

The powder should be reconstituted only by introducing the provided solvent contained in the syringe into the vial.

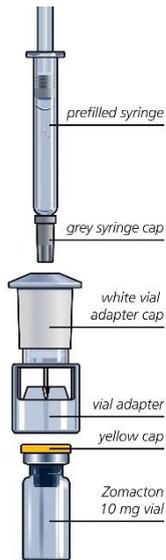
See the package leaflet for detailed instructions for reconstitution.

The following is a general description of the reconstitution and administration process. Reconstitution should be performed in accordance with good practice rules, particularly in the respect of asepsis.

1. Hands should be washed.
 2. Flip off the yellow plastic protective caps from the vial.
 3. The top of the vial should be wiped with an antiseptic solution to prevent contamination of the content.
 4. Place the vial adaptor or the solvent transfer connector over the centre of the vial with the spike facing downwards then push down firmly until it clicks into place. Remove the adaptor cap.
 5. Take the syringe. Remove the grey cap. Place the syringe into the adaptor / connector of the vial and inject the solvent slowly into the vial aiming the stream of liquid against the glass wall in order to avoid foam.
 6. Place the adaptor cap / connector cap back on the adaptor / connector.
 7. Gently swirl the vial a few times until the content is completely dissolved. Do not shake; this may cause denaturation of the active substance.
 8. If the solution is cloudy or contains particulate matter, it should not be used. In the case of cloudiness after refrigeration, the product should be allowed to warm to room temperature. If cloudiness persists, discard the vial and its contents.
- The content must be clear and colourless after reconstitution.

Any unused product or waste material should be disposed of in accordance with local requirements.

Reconstitution with vial adaptor for use with ZomaJet 10 device



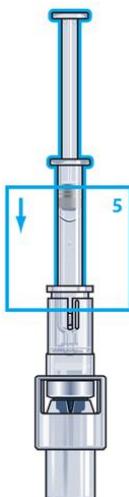
Step 1
Remove the yellow cap from the ZOMACTON vial.



Step 2
Place the vial adaptor over the centre of the vial with the spike facing downwards. Push down firmly until it clicks into place.



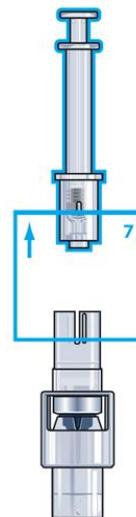
Step 3 and 4
Remove the grey syringe cap and also remove the white vial adaptor cap.



Step 5
Place the vial on a flat surface and hold the vial adaptor. Place the syringe into the vial adaptor and push down.



Step 6
Press the syringe plunger slowly. Ensure that all the solution goes into the vial.



Step 7
Hold the vial and firmly pull the syringe away. The syringe adaptor will remain in place.



Step 8
Place the white vial adaptor cap back on the adaptor by pushing firmly until it clicks into place.

The vial must then be swirled gently until the powder has dissolved completely to form a clear, colourless solution.

Place the reconstituted vial of ZOMACTON in an upright position in the refrigerator at 2°C to 8°C.

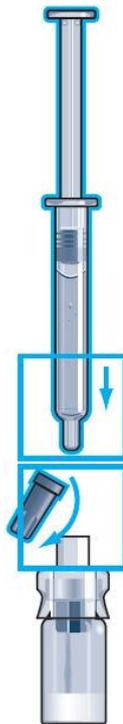
Avoid shaking or vigorous mixing. If the solution remains cloudy or contains particles, the vial and its contents should be discarded. In case of cloudiness after refrigeration, the solution should be allowed to warm up to room temperature. If cloudiness still persists, discard the vial and its contents.

Reconstitution with solvent transfer connector for injection with an ordinary syringe



Step 1

Remove the yellow cap from the ZOMACTON vial. Place the solvent transfer connector over the centre of the vial with the spike facing downwards. Push down firmly until it clicks into place.



Step 2

Remove the grey syringe cap.



Step 3

Place the vial on a flat surface and hold the solvent transfer connector. Place the syringe into the solvent transfer connector and push down firmly. Press the syringe plunger slowly. Ensure that all the solution goes into the vial.



Step 4

Hold the vial and firmly pull the syringe away. The solvent transfer connector will remain in place. Place the cap on the solvent transfer connector.

Step 5

The vial must then be swirled gently until the powder has dissolved completely to form a clear, colourless solution.

Place the reconstituted vial of ZOMACTON in an upright position in the refrigerator at 2°C to 8°C.

Avoid shaking or vigorous mixing. If the solution remains cloudy or contains particles, the vial and its contents should be discarded. In case of cloudiness after refrigeration, the

solution should be allowed to warm up to room temperature. If cloudiness still persists, discard the vial and its contents.

7. MARKETING AUTHORISATION HOLDER

Ferring Ireland Ltd
United Drug House
Magna Drive
Magna Business Park
Citywest Road
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PA 1009/8/3

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th December 2008
Date of last renewal: 15th June 2011

10. DATE OF REVISION OF THE TEXT

August 2019