SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zomacton 4 mg, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains :

Somatropin* …..…….4 mg
(corresponding to a concentration of 1.3 mg/ml or 3.3 mg/ml after reconstitution)

* produced in *Escherichia coli* cells by recombinant DNA technology.

Excipient with known effect (in the solvent):
Benzyl alcohol: 9 mg/ml

For the 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 powder. The solvent in ampoule is clear and colorless.

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 and for the long-term treatment of growth retardation due to Turner's Syndrome confirmed by chromosome analysis.

4.2 Posology and method of administration

Posology

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 and schedule 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.

Growth Hormone Deficiency
Generally, a dose of 0.17 - 0.23 mg/kg bodyweight (approximating to 4.9 mg/m^2 – 6.9 mg/m^2 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/m^2 body surface area). The total weekly dose of 0.27 mg/kg or 8 mg/m^2 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/m^2/body surface area) per week divided into 6 - 7 s.c. injections is recommended (corresponding to daily injections of 0.05 mg/kg/bodyweight or 1.40-1.63 mg/m^2/body surface area).

<u>Method of administration</u>
The required ZOMACTON dose is administered by using the Ferring-Pen (a needle device) or alternatively a conventional syringe.

Specific instructions for use of the Ferring-Pen are given in a brochure supplied with the device.

The clear, colourless solution should then be administered subcutaneously.

Following reconstitution, the following steps should be performed for injection

1. Hands should be washed.
2. The top of the vial should be wiped with an alcohol swab to prevent contamination of the content. Do not touch the rubber stopper after cleaning.
3. Turn the vial upside down keeping the top of the needle below the surface of the medication. Gently pull back on the plunger until your prescribed amount of medication fills the syringe. If you do not have enough medication for a full dose, reconstitute a new vial to make up the difference.
4. With the needle still in the upside down vial, gently tap the syringe to loosen any air bubbles.
5. Remove the needle from the vial and carefully replace the needle cap until ready to inject.
6. Thoroughly clean the injection site with an alcohol swap.

7. Check that the correct dose is in the syringe.
8. Remove the needle cap and hold the syringe the way you hold a pencil.
9. With your free hand, gently pinch the skin around the injection site between your fingers.
10. Insert the needle into the tissue beneath the skin's surface at a 45° to 90° angle to reduce discomfort.
11. Holding the syringe in place, pull back (if there is blood in the syringe, it means you have entered a blood vessel. Do not inject ZOMACTON. Withdraw the needle, discard all supplies, and go back to step 1. Choose and clean a new injection site). If no blood appears, slowly push the plunger until the syringe is empty.
12. Quickly pull the needle straight out and apply pressure to the site of injection with a sterile gauze pad. Throw away the needle and syringe in your sharps disposable container.

Do not share your syringes, needles, or vials with anyone else. You may give them an infection or get one from them.

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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Zomacton must not be given to premature babies or neonates as the solvent contains benzyl alcohol.

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

Zomacton 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 Zomacton.

In children with chronic renal disease, treatment with Zomacton 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).

Due to the presence of benzyl alcohol as excipient, ZOMACTON may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old and must not be given to premature babies or neonates.

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.

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 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.

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.

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may, as such, unmask incipient 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.

Because somatropin may reduce insuline sensitivity , patients should be monitored for evidence of glucose intolerance. For patients with diabetes mellitus, the insuline 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.

Introduction of somatropin treatment may result in inhibition of 11βHSD-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).

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

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.

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.

Pancreatitis

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

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

Pregnancy
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.

Breastfeeding
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

Zomacton has no or negligible 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 at the injection site. On rare occasions patients have developed pain and an itchy rash at the site of injection.

System Organ Class	Very Common (≥ 1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000, to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)
Blood and lymphatic system disorders			anemia		
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 hyperglyca	(children) glucose tolerance	hypoglycaemia, hyperphosph	diabetes mellitus type II	

	emia	impaired	atemia		
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, 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 in 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 the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

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.

Mechanism of action
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 by s.c. injection. Peak plasma levels of around 17 ng/ml were observed approximately 4 hours after administration of the medicinal product. The apparent volume of distribution (V/F) for somatropin was 48 litres, the apparent clearance (CL/F) was 15 L/h and a terminal half-life of 2.2 hours was observed.
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

Single dose toxicity:
Single dose toxicity studies were performed in rats (intramuscular application of 10 mg/kg), dogs and monkeys (intramuscular dose of 5 mg/kg, corresponding to the 50 - 100 fold of the human therapeutic dose). There was no evidence of drug-related toxicity in any of these species.

Repeated dose toxicity:
No relevant toxicological signs were observed in a rat study in which doses of 1.10 mg/kg/day for 30 days and 0.37 mg/kg/day for 90 days were administered to the animals.

Reproduction toxicology, mutagenic and carcinogenic potential
Somatropin produced by recombinant DNA technology is identical to endogenous human pituitary growth hormone. It has the same biological properties and it is usually administered in physiological doses. Therefore, it was not deemed necessary to perform the full range of such toxicological studies. Untoward effects on reproduction organs, on pregnancy and lactation are unlikely and also no carcinogenic potential has to be expected. A mutagenicity study showed the absence of mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Mannitol

Solvent
Sodium chloride
Benzyl alcohol
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 may be stored for a maximum of 14 days in a refrigerator (2 °C-8 °C).
Store the vial in an upright position.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Powder in vial (type I glass) with a stopper (grey halobutyl rubber), a seal and a “flip-off” top + 3.5 ml solvent in ampoule (type I glass):
Pack size of 1, 5 and 10
or

Powder in vial (type I glass) with a stopper (grey halobutyl rubber), a seal and a “flip-off” top + 3.5 ml solvent in ampoule (type I glass), a syringe (polypropylene) with a plunger (polypropylene), a seal, and needle (stainless steel)
Pack size of 5
or

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitution
The powder should only be dissolved with the solvent provided.

Two concentrations can be prepared depending on the volume of solvent used

- for administration using a syringe or Ferring-Pen (not provided in the packaging), use 1.3 ml of solvent for a concentration of 3.3 mg/ml (taking into account the whole content of the vial which is greater than 4 mg).
- use 3.2 ml of solvent for a concentration of 1.3 mg/ml. (taking into account the whole content of the vial which is greater than 4 mg).

Reconstitution of the powder with the solvent, and administration of the solution for injection should be undertaken using syringe and needle.

Reconstitution should be performed in accordance with good practice rules, particularly in the respect of asepsis.

1. Hands should be washed
2. Fit the needle into the graduated syringe. Remove the plastic top on the vial. The top of the vial should be wiped with an alcohol swab to prevent contamination of the content. Do not touch the rubber stopper after cleaning.
3. Snap off the top of the solvent ampoule. Remove the plastic cover on the needle. Make sure that the plunger is completely pushed in before introducing the needle into the ampoule.
4. Slowly draw up the required volume in the syringe.
5. Place the needle into the centre of the clean rubber stopper and into 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. Throw away the syringe and needle into a sharps disposal container
7. The vial must then be swirled with a gentle rotary motion until the contents are completely dissolved in order to obtain a clear and colourless solution.

Since the powder mainly contains proteins, shaking or vigorous mixing is not recommended. If after mixing, the solution is cloudy or contains particles, the vial and its contents should be disposed of.
In case of cloudiness after refrigeration, the solution should be allowed to warm up to room temperature (25°C). If cloudiness still persist or coloration appears, dispose of the vial and its contents.
The solution should be used within 14 days after reconstitution if stored in a refrigerator.
Any unused solution in the vial should be disposed of at the end of the 14-day storage period.

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

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 03194/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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