מקרא צבעים

XX- מידע חדש המהווה החמרה.

בתכלת סומן מידע המהווה התאמה לתנאי רישום בישראל

כל השינויים מסומנים ב **track changes**

1. NAME OF THE MEDICINAL PRODUCT

ZOMACTON 10 mg~~/ml, powder and solvent for solution for injection in pre-filled syringe.~~
ZOMACTON 4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOMACTON 10 mg:
Somatropin* …..……..10 mg
(10 mg/ml after reconstitution for one vial)
* Produced in E*scherichia coli* cells using recombinant DNA technology

ZOMACTON 4 mg:
Somatropin* …..……..4 mg
(corresponding to a concentration of 1.3 mg/ml or 3.3 mg/ml after reconstitution)
* Produced in E*scherichia coli* cells using recombinant DNA technology
Excipient with known effect (in the solvent): Benzyl alcohol: 9 mg/ml

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection ~~in pre-filled syringe~~.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

~~Zomacton is indicated for:~~

Children:
Short stature due to inadequate or failed secretion of pituitary growth hormone or Turner's syndrome.
Short stature in children with renal insufficiency.

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/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 are recommended (corresponding to daily injection of 0.05 mg/kg/bodyweight or 1.40-1.63 mg/m^2/body surface area).

Instructions for preparation, see section 6.6.

Administration

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

Specific instructions for the use of the ZOMAJET ~~VISION X~~ device are given in a booklet supplied with the device.

4.3 Contraindications

- Zomacton 4 mg must not be given to premature babies or neonates as the solvent
- contains benzyl alcohol.
- Hypersensitivity to somatropin or to any of the excipients.
- Somatropin must not be used when there is any evidence of activity of a tumor. Intracranial tumors must be inactive and antitumor therapy must be completed prior to

starting GH therapy. Treatment should be discontinued if there is evidence of tumor growth.

- Somatropin~~Zomacton~~ should not be used 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 somatropin ~~(see section 4.4)~~.
- In children with chronic renal disease, treatment with somatropin 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).
Zomacton 10 mg - 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.
Zomacton 4 mg - 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 4mg and Zomacton 10mg:

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.

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 lesion

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 ~~Zomacton~~

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 ~~Vision X~~ 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.
~~In all patients developing other or similar acute critical illness, the possible benefit of treatment with growth hormone must be weighed against the possible risk involved.~~

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.

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 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~~e~~ is not recommended during pregnancy and in women 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

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

System Organ Class	Very Common (> 1/10)	Common (>1/100, <1/10)	Uncommon (>1/100. <1/1,000)	Rare (>1/1,000, <1/10,000)	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	diarrhea	
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 hemorrhage, injection site mass, hypertrophy		
Immune system disorders		antibody building			
Investigations				renal function test abnormal	
Metabolism and nutrition disorders	(adult) mild hyperglycemia	(children) glucose tolerance impaired	hypoglycemia, 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		

Formatted: English (United States)

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 titers 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.

~~Rare cases of benign intra-cranial hypertension have been reported with somatropin (see section 4.4).~~

~~System Organ Class~~	~~Very Common (> 1/10)~~	~~Common (>1/100, <1/10)~~	~~Uncommon (>1/100. <1/1,000)~~	~~Rare (>1/1,000, <1/10,000)~~	~~Very rare (<1/10,000)~~
~~Blood and lymphatic system disorders~~	-	-	~~anemia~~	-	-
~~Cardiac disorders~~	-	-	~~tachycardia, (adult) hypertension~~	~~(children) hypertension~~	-
~~Ear and labyrinth disorders~~	-	-	~~vertigo~~	-	-
~~Endocrin disorders~~	-	~~hypothyroidism~~	-	-	-
~~Eye disorders~~	-	-	~~papilloedema, diplopia~~	-	-
~~Gastroinyestinal 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	-	-

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

Formatted: English (United Kingdom)

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

Zomacton 10mg: Twenty-four (24) healthy adult subjects received 1.67 mg somatropin either by conventional S.C. injection or by ZomaJet ~~Vision~~ 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 ~~vision~~ 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.
Zomacton 4 mg:
Eight healthy subjects received 0.1 mg somatropin/kg body weight. Peak plasma levels of about 64 ng/ml were found 6 hours after administration.

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.

~~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

Zomacton 10mg:

Powder

Mannitol
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate

Solvent

m-cresol
Water for injections

Zomacton 4mg:

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

The expiry date of the product is indicated on the packaging materials.
~~3 years~~
After reconstitution, store vials in an upright position.
Zomacton 10mg:
After reconstitution, the solution must be stored for a maximum of 28 days in a refrigerator at 2° C - 8° C.
Zomacton 4mg:
After reconstitution, the solution must be stored for a maximum of 14 days in a refrigerator at 2° C - 8° C.

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 condition of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Zomacton 10 mg is supplied in sets ~~for use with the needle-free device Zomajet Vision X~~containing: 1 type I glass vial with powder, 1 type I glass prefilled syringe with solvent and 1 vial adaptor
~~Powder: Vial (type I glass) with closure (rubber, halobutyl polymer) in combination with an aluminium seal and "Flip-off" cap (plastic).~~
~~Solvent: Pre-filled 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.~~
Zomacton 4mg is supplied in set containing: 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).

6.6 Special precautions for disposal

Reconstitution
The powder should be reconstituted only ~~by introducing~~with the ~~provided~~ solvent provided~~contained in the prefilled syringe into the vial~~.
See the package leaflet for detailed instructions for reconstitution.

Zomacton 4mg: two concentrations can be prepared depending on the volume of solvent used:

- for administration using a syringe, ZomaJet 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)
- for administration using a syringe only, 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)

Formatted: Bulleted + Level: 1 + Aligned at: 0.63 cm + Indent at: 1.27 cm

Formatted: Bulleted + Level: 1 + Aligned at: 0.63 cm + Indent at: 1.27 cm

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 cap~~s~~ 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. Zomacton 10 mg: Take the prefilled syringe.
Zomacton 4 mg: Fill the syringe with the solvent (for injection with Zomajet use 1.3 ml solvent for concentration 3.3mg/ml, for administration with syringe use 3.3 ml solvent for concentration 1.3 mg/ml)

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.

7. MANUFACTURER

Ferring, Kiel Germany

8. LICENSE HOLDER
Ferring Pharmaceuticals Ltd., 8 HASHITA ST, IND. PARK CAESAREA 3088900 Israel

9. **LICENSE NUMBER**
Zomacton 10mg: 144-21-31997-00
Zomacton 4mg: 032-64-25442-00

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved on December 2016 and updated according to the Ministry of Health order on July 2019.

Formatted: English (United States)