ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Valtropin 5 mg/1.5 ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 5 mg somatropin (corresponding to 15 IU).

After reconstitution with 1.5 ml solvent, 1 ml contains:
somatropin* 3.33 mg (corresponding to 10 IU)
* produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White or almost white powder. The solvent is a clear solution.

After reconstitution with the solvent provided, Valtropin has a pH of approximately 7.5 and an osmolality of approximately 320 mOsm/kg.

Medicinal product no longer authorised

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paediatric population
- Long-term treatment of children (2 to 11 years old) and adolescents (12 to 18 years old) with growth failure due to an inadequate secretion of normal endogenous growth hormone.
- Treatment of short stature in children with Turner syndrome, confirmed by chromosome analysis.
- Treatment of growth retardation in pre-pubertal children with chronic renal insufficiency.

Adult patients
- Replacement therapy in adults with pronounced growth hormone deficiency of either childhood- or adult-onset aetiology.

Patients with severe growth hormone deficiency in adulthood are defined as patients with known hypothalamic-pituitary pathology and at least one additional known deficiency of a pituitary hormone not being prolactin. These patients should undergo a single dynamic test in order to diagnose or exclude a growth hormone deficiency. In patients with childhood-onset isolated growth hormone deficiency (no evidence of hypothalamic-pituitary disease or cranial irradiation), two dynamic tests should be recommended, except for those having low insulin-like growth factor-1 (IGF-1) concentrations (< 2 standard deviation score (SDS)), who may be considered for one test. The cut-off point of the dynamic test should be strict.

4.2 Posology and method of administration

Therapy with Valtropin should be initiated and monitored by physicians adequately experienced in the diagnosis and management of patients with growth hormone deficiency.

Posology

The dosage and administration schedule should be individualised for each patient.

Dosage in paediatric population

Growth hormone deficiency in children
The recommended dosage is 0.025 - 0.035 mg/kg body weight per day.

Children with Turner syndrome
The recommended dosage is 0.045 - 0.050 mg/kg body weight per day, given as a subcutaneous injection.

Pre-pubertal children with chronic renal insufficiency
The recommended dosage is 0.045 - 0.050 mg/kg body weight per day, given as a subcutaneous injection.

Dosage in adult patients

Growth hormone deficiency in adults
The recommended starting dose is 0.15 - 0.30 mg/day, given as a subcutaneous injection. A lower starting dose may be necessary in older and obese patients.

This dose should be gradually increased according to individual patient requirements based on the clinical response and serum IGF-1 concentrations. Total daily dose usually does not exceed 1 mg. IGF-1 concentrations should be maintained below the upper limit of the age-specific normal range.

The minimum effective dose should be used.

The dosage of somatropin should be decreased in cases of persistent oedema or severe paresthesia, in order to avoid the development of carpal tunnel syndrome.

Experience of prolonged treatment (over 5 years) with somatropin in adults is limited.

Special populations

Elderly
Experience of somatropin treatment in patients above 60 years of age is limited. A lower starting dose may be necessary in older patients. Dose requirements may decline with increasing age.

Renal impairment
Currently available data on renal insufficiency are described in section 4.4, but no recommendation on a posology can be made.

Hepatic impairment
In patients with severe liver dysfunction a reduction of somatropin clearance has been noted. The clinical significance of this decrease is unknown.

Method of administration

Valtropin is administered by subcutaneous injection.

The injection sites should be varied in order to avoid lipo-atrophy.

For further information on reconstitution and administration see section 6.6.

4.3 Contraindications

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- Hypersensitivity to the active substance or to any of the excipients (e.g. metacresol) (see section 4.4).
- 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.
- Valtropin should not be used for growth promotion in children with closed epiphyses.
- Patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or patients having acute respiratory failure.

4.4 Special warnings and precautions for use

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

Pituitary
There is no evidence to suspect that growth hormone replacement influences the recurrence rate or regrowth of intracranial neoplasms, but standard clinical practice requires regular pituitary imaging in patients with a history of pituitary pathology. A baseline scan is recommended in these patients before instituting growth hormone replacement therapy.

Tumour control
If the patient has had a brain tumour, the patient should be re-examined frequently to make sure that the tumour has not come back.
In childhood cancer survivors, a higher risk of a second neoplasm (benign or malignant) has been reported in patients treated with somatropin. Intracranial tumours, in particular, were the most common of these second neoplasms.

Intracranial hypertension
In cases of severe or recurrent headache, visual problems, nausea, and/or vomiting, a fundoscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, the growth hormone treatment should be discontinued. 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.

Insulin sensitivity
Because human growth hormone may induce a state of insulin resistance, patients treated with somatropin should be monitored for evidence of glucose intolerance.

Thyroid function
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.

Slipped capital epiphyse
Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently. Any child with the onset of a limp during growth hormone therapy should be evaluated.

Growth hormone deficiency after epiphyseal closure
Subjects who had been treated with growth hormone during childhood, until final height was attained, should be re-evaluated for growth hormone deficiency after epiphyseal closure before replacement therapy is commenced at the doses recommended for adults.

Treatment after the end of growth in children

Medicinal product no longer authorised

For children, the treatment should be continued until the end of the growth has been reached. It is advisable not to exceed the recommended dosage in view of the potential risks of acromegaly, hyperglycaemia, and glucosuria.

Prader-Willi syndrome
Valtropin is not indicated for the treatment of patients with growth failure due to Prader-Willi syndrome unless they also have a diagnosis of growth hormone deficiency. There have been reports of sleep apnoea and sudden death after initiating growth hormone therapy in 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.

Renal insufficiency
Before instituting treatment with somatropin for growth retardation secondary to chronic renal insufficiency, children should have been followed for one year to verify growth disturbance. Conservative treatment for renal insufficiency (which includes control of acidosis, hyperparathyroidism, and nutritional status for one year prior to the treatment) should have been established and should be maintained during treatment. Treatment with somatropin should be discontinued at the time of renal transplantation.

Gender and dosing
In order to reach the defined treatment goal, men may need lower growth hormone doses than women. Oral oestrogen administration increases the dose requirements in women. An increasing sensitivity to growth hormone (expressed as change in IGF-1 per growth hormone dose) over time may be observed, particularly in men. The accuracy of the growth hormone dose should therefore be controlled every 6 months.

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

Pancreatitis in children
Children treated with somatropin have an increased risk of developing pancreatitis compared to adults treated with somatropin. Although rare, pancreatitis should be considered in somatropin-treated children who develop abdominal pain.

Accidental intramuscular injection
After accidental intramuscular injection, hypoglycaemia may appear. Any unwanted reaction should be followed. No special treatment is recommended.

Sensitivity to metacresol
Valtropin should not be reconstituted with the supplied solvent for patients with a known sensitivity to metacresol. If sensitivity to the accompanying solvent occurs, the vials should be reconstituted with water for injections and used as a single use vial (see section 6.3).

Medicinal product no longer authorised

4.5 Interaction with other medicinal products and other forms of interaction

Excessive glucocorticoid therapy will inhibit the growth-promoting effect of human growth hormone. Patients with co-existing adrenocorticotropic hormone (ACTH) deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

In women taking oral oestrogens, a higher dose of somatropin may be required to achieve the treatment goal.

Patients taking insulin for diabetes mellitus should be carefully monitored during treatment with somatropin. An adjustment of the insulin dose may be required.

Data from an interaction study performed in growth hormone 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 P 450 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and cyclosporine) 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 Valtropin no clinical data on exposed pregnancies are available. Animal studies are insufficient with respect to effects on pregnancy, embryofoetal development, parturition or postnatal development (see section 5.3). Therefore Valtropin should not be used during pregnancy unless clearly necessary.

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

Fertility
No data on fertility are available. Animal data showed no effect on fertility parameters.

4.7 Effects on ability to drive and use machines

Valtropin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common frequent adverse reactions are associated with the injection site, of endocrine nature, and headache, paresthesia and joint pain and disorder (arthralgia) in adults.

During clinical studies 128 children (98 children with growth hormone deficiency and 30 with Turner syndrome) were exposed to Valtropin. The safety profile of Valtropin observed in these clinical studies was consistent with that reported with the reference medicinal product used in these studies and other somatropin containing medicinal products.

The following adverse reactions and their frequencies have been observed under treatment with somatropin based on published information:

Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data), including isolated reports

Tabulated summary of adverse reactions

Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon: Neoplasm malignant, neoplasm
Blood and lymphatic system disorders	Uncommon: Anaemia
Immune system disorders	Common: Antibody building
	Not known: Single case of acute hypersensitivity involving urticaria and pruritus
Endocrine disorders	Common: Hypothyroidism
Metabolism and nutrition disorders	Common: Glucose tolerance impaired
	Common: Mild hyperglycaemia (1% in children;

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	1% - 10% in adults)
	Uncommon: Hypoglycaemia, hyperphosphatemia
	Rare: Diabetes mellitus
	Not known: Insulin resistance
Psychiatric disorders	Uncommon: Personality disorder
Nervous system disorders	Very common: Headache in adults
	Very common: Paresthesia in adults
	Common: Hypertonia
	Common: Insomnia in adults
	Common: Carpal tunnel syndrome in adults
	Uncommon: Carpal tunnel syndrome in children
	Uncommon: Nystagmus
	Rare: Neuropathy, intracranial pressure increased
	Rare: Benign intracranial hypertension
	Rare: Paresthesia in children
	Very rare: Insomnia in children
Eye disorders	Uncommon: Papilloedema, diplopia
Ear and labyrinth disorders	Uncommon: Vertigo
Cardiac disorders	Common: Hypertension in adults
	Uncommon: Tachycardia
	Rare: Hypertension in children
Respiratory, thoracic and mediastinal disorders	Common: Dyspnoea in adults
	Common: Sleep apnoea in adults
Gastrointestinal disorders	Uncommon: Vomiting, abdominal pain, flatulence, nausea
	Rare: Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon: Lipodystrophy, skin atrophy, exfoliative dermatitis, urticaria, hirsutism, skin hypertrophy
Musculoskeletal and connective tissue disorders	Very common: Arthralgia in adults
	Common: Arthralgia in children
	Common: Myalgia
	Uncommon: Muscle atrophy, bone pain
Renal and urinary disorders	Uncommon: Urinary incontinence, haematuria, polyuria, urine frequency/pollakiuria, urine abnormality
Reproductive system and breast disorders	Uncommon: Genital discharge
	Uncommon: Gynaecomastia in adults
	Very rare: Gynaecomastia in children
General disorders and administration site conditions	Very common: Oedema, peripheral oedema in adults
	Common: Oedema, peripheral oedema in children
	Common: Injection site reactions, asthenia
	Uncommon: Injection site atrophy, injection site haemorrhage, injection site mass, hypertrophy, weakness in children
Investigations	Rare: Renal function test abnormal

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Description of selected adverse reactions

In a clinical study with Valtropin, 3% of children with growth hormone deficiency developed antibodies to somatropin. The binding capacity of these antibodies was low and there was no effect on growth rate. Testing for antibodies to somatropin should be carried out in any patient who fails to respond to therapy.

Anti-host cell protein (anti-*S. cerevisiae*) antibodies were uncommon in patients treated with Valtropin. The generation of such antibodies with low binding capacity is unlikely to be clinically relevant. In contrast to bacteria (*E. coli*), yeast has not been described to elicit adjuvant effects modifying the immunological response.

Paediatric population
Mild and transient oedema was observed early during the course of treatment with somatropin.

Adult patients
In adult patients with adult-onset growth hormone deficiency, oedema, muscle pain, joint pain and disorders were reported early in therapy and tended to be transient.

4.9 Overdose

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Long-term overdose could result in signs and symptoms of acromegaly consistent with the known effects of excess human growth hormone. Treatment is symptomatic and supportive. There is no antidote for somatropin overdose. It is recommended to monitor thyroid function following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and somatropin agonists; ATC code: H01AC01

Somatropin is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the medicinal product is identical to that of human growth hormone of pituitary origin. Valtropin is synthesised in yeast cells (*Saccharomyces cerevisiae*).

The biological effects of somatropin are equivalent to those of human growth hormone of pituitary origin.

The most prominent effect of somatropin is that it stimulates the growth plates of long bones. Additionally, it promotes cellular protein synthesis and nitrogen retention.

Somatropin stimulates lipid metabolism; it increases plasma fatty acids and high-density lipoprotein (HDL)-cholesterols, and decreases total plasma cholesterol.

Somatropin therapy has a beneficial effect on body composition in growth hormone-deficient patients, in that body fat stores are reduced and lean body mass is increased. Long-term therapy in growth hormone-deficient patients increases bone mineral density.

Somatropin may induce insulin resistance. Large doses of somatropin may impair glucose tolerance.

Clinical studies

The efficacy and safety of Valtropin has been assessed in a randomised, double-blind, parallel, controlled Phase III study in children with growth hormone deficiency. There were no relevant

Medicinal product no longer authorised

differences between Valtropin and the reference medicinal product with regard to height velocity and height velocity SDS.

An open single-arm Phase III study investigating the efficacy and safety of treatment with Valtropin in girls with short stature associated with Turner syndrome showed a significant effect of study treatment on height velocity.

5.2 Pharmacokinetic properties

A double-blind, randomised, single dose, crossover study in 24 healthy volunteers showed that the pharmacokinetic profile of Valtropin was comparable to that of the reference medicinal product. Subcutaneous administration of 0.073 mg/kg body weight of Valtropin resulted in a C_{max} of 43.97 ng/ml and an $AUC_{0\text{-}24\,h}$ of 369.90 ng·h/ml. C_{max} was reached at 4 h and $t_{½}$ was 3 h.

5.3 Preclinical safety data

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

Animal studies with Valtropin are not sufficient to assess the reproductive toxicity potential. From reproductive toxicity studies performed with other somatropin medicinal products there is no evidence of an increased risk of adverse reactions for the embryo or foetus.

Long-term studies for carcinogenicity have not been performed. There are no specific local tolerance studies in animals after subcutaneous injection of Valtropin. However, in single and repeat-dose general toxicity studies no adverse reactions at the injection sites were reported.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Glycine
Mannitol
Sodium dihydrogen phosphate anhydrous
Disodium phosphate anhydrous
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment).

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

<u>After first opening or following reconstitution with the solvent provided:</u>
After reconstitution with the solvent provided, chemical and physical in-use stability has been demonstrated for 21 days at 2°C - 8°C (refrigerator).

Following reconstitution with water for injections:
After reconstitution with water for injections, the medicinal product must be used immediately and must be used as a single use vial. If not used immediately, in-use storage times and conditions prior to use would normally not be longer than 24 hours at 2°C - 8°C (refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

For the purpose of transport and/or ambulatory use, the non-reconstituted medicinal product can be kept at room temperature (not above 25°C) for one single period of up to 4 weeks before use.
The date of refrigerator removal and the new expiry date should be written on the outer carton. At the end of the new expiry date, the medicinal product should have been used or be disposed of.

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

6.5 Nature and contents of container

5 mg of powder in a vial (Type I glass) closed with a stopper (butyl rubber) and a flip-off cap (aluminium plastic).
1.5 ml of solvent in a pre-filled syringe (Type I glass) closed with a tip cap (FluroTec coated butyl rubber)

Pack size of 1 vial and 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

Detailed instructions for the handling of the medicinal product are given at the end of the package leaflet.

For use and handling

Valtropin should not be reconstituted with the supplied solvent for patients with a known sensitivity to metacresol (see section 4.3). If sensitivity to the accompanying solvent occurs, the vials should be reconstituted with water for injections and used as a single use vial.

Reconstitution with the solvent provided
Each vial of Valtropin should be reconstituted using the accompanying solvent. The solvent should not be used if it is discoloured or cloudy. The solvent should be injected into the vial by aiming the stream of liquid against the glass wall. Following reconstitution, the vial should be swirled with a GENTLE rotary motion until the contents are completely dissolved. DO NOT SHAKE. The resulting solution should be clear, without particulate matter. If the solution is discoloured, cloudy or contains particulate matter, the contents MUST NOT be injected. Before and after every injection, the septum of the vial should be wiped with alcohol to prevent contamination of the contents by repeated needle insertions. If reconstituted with the solvent, then the solution is for multidose use (see section 6.3).

Reconstitution with water for injections
After reconstitution with water for injections the medicinal product must be used immediately (see section 6.3) and the solution is for single use only.

Administration
Sterile disposable syringes and needles should be used for administration of Valtropin. The volume of the syringe should be small enough so that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

Medicinal product no longer authorised

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

7. MARKETING AUTHORISATION HOLDER

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/335/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation 24.04.2006
Date of latest renewal 24.04.2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

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ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

LG Life Sciences Ltd., Iksan Plant, 601 Yongje-dong, Iksan-si, Jeonbuk-do 570-350, South Korea

Name and address of the manufacturer responsible for batch release

BioPartners GmbH, Kaiserpassage 11, D-72764 Reutlingen, Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH should submit an updated Risk Management Plan reflecting: New neoplasm, Second neoplasm in childhood cancer survivors and Intracranial aneurysm and Intracranial haemorrhage as potential risk. The Risk Management plan should be submitted by 9 May 2012.

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.1 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Valtropin 5 mg/1.5 ml powder and solvent for solution for injection
somatropin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial of powder contains 5 mg (15 IU) somatropin (3.33 mg/ml somatropin after reconstitution with 1.5 ml solvent).

3. LIST OF EXCIPIENTS

Powder: glycine, mannitol, sodium phosphate monobasic, sodium phosphate dibasic.
pH adjustment: sodium hydroxide and hydrochloric acid.

Solvent: metacresol (see leaflet for further information) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
1 vial of 5 mg powder
1 pre-filled syringe of 1.5 ml solvent.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For information on reconstitution and use read the package leaflet.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution with the solvent provided: can be stored for 21 days in a refrigerator.
After reconstitution with water for injections: must be used immediately.

Medicinal product no longer authorised

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioPartners GmbH, Kaiserpassage 11, D-72764 Reutlingen, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/335/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Valtropin 5 mg/1.5 ml

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Valtropin 5 mg/1.5 ml powder for solution for injection
somatropin

Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg (15 IU)

6. OTHER

Store in a refrigerator. Do not freeze.

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE OF SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Valtropin

Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 ml (water for injections with metacresol)

6. OTHER

Store in a refrigerator. Do not freeze.

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Medicinal product no longer authorised

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valtropin 5 mg/1.5 ml powder and solvent for solution for injection
Somatropin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

Medicinal product no longer authorised

1. WHAT Valtropin IS AND WHAT IT IS USED FOR

Your medicine is called Valtropin. It is a human growth hormone, also called somatropin. It has the same structure as the growth hormone that the body produces in the pituitary glands (glands located at the base of the brain). Growth hormone regulates the growth and development of cells. When it stimulates growth of cells in the long bones of the legs and spine, it causes an increase in height.

Valtropin is used
- to treat children (2 to 11 years old) and teenagers (12 to 18 years old) who do not develop to their normal height because of poor bone growth caused by growth hormone deficiency (relative lack of growth hormone), Turner syndrome, or 'chronic renal insufficiency' (a condition in which the kidneys gradually lose their ability to perform their normal functions, such as the removal of wastes and extra fluid from the body).
- to treat adults with severe growth hormone deficiency who already had growth hormone deficiency when they were children or who do not have enough growth hormone during their adult years for some other reason.

In this leaflet the patient is addressed as 'you'. Caregivers administering Valtropin to their children should consider that 'you' refers to the child.

2. BEFORE YOU USE Valtropin

Do not use Valtropin
- if you are **allergic (hypersensitive) to somatropin or any of the other ingredients of the powder or solvent of Valtropin**, e.g. metacresol (see section 2, 'Take special care with Valtropin – Occurrence of certain side effects')
- and tell your doctor if you have **an active tumour**. Tumours must be inactive and you must have finished your anti-tumour treatment before you start your treatment with Valtropin.
- for growth promotion in children who have already **stopped growing**
- if you have had a **serious heart or abdominal operation**
- if you are **being treated for more than one injury following a serious accident**
- if you have **sudden serious breathing problems**

Take special care with Valtropin

Examinations before starting treatment

- A specialist doctor trained in hormone disorders must examine you to decide if it is safe to use Valtropin.
- If you have had a brain tumour a specialist doctor trained in hormone disorders must examine your pituitary function to decide if it is safe to use Valtropin.
- Before children are treated for growth hormone deficiency due to kidney problems, the doctor should observe the child for one year before starting growth hormone treatment.
- If adults have been treated with growth hormone during childhood, they should be re-evaluated for growth hormone deficiency before starting any further treatment with growth hormones.
- Patients with Prader-Willi syndrome should not be treated with Valtropin unless they are also suffering from growth hormone failure.

During or after serious illness

- If you have had a brain tumour, you should be re-examined frequently to make sure that the tumour has not come back.
- If you had cancer as a child. A higher risk for having a second tumour (benign and malignant) has been reported in patients that survived their cancer and were treated with somatropin. Of these second tumours, in particular, brain tumours were the most common.
- If children have had a kidney transplant, growth hormone treatment will be stopped.
- If the child has Turner syndrome, the child's doctor should carefully check for ear infections such as otitis media, because Turner syndrome patients have an increased risk of ear or other hearing disorders.

Occurrence of certain side effects

- If symptoms like headache (severe and recurrent), visual changes, nausea and/or vomiting occur, please ask your doctor for advice.
- If you have injected Valtropin by mistake into the muscle instead of under the skin, your blood sugar may become too low (hypoglycaemia). Please contact your doctor for further advice.
- If the child begins to limp under treatment with Valtropin, please ask your doctor for advice.
- If you are a child and you are treated with somatropin. You have an increased risk of developing an inflammation of your pancreas (pancreatitis) compared to adults treated with somatropin. Although rare, pancreatitis should be considered in somatropin-treated children who develop abdominal pain.
- Too much growth hormone can cause greater than normal growth of ears, nose, lips, tongue and cheekbone (acromegaly), high blood sugar (hyperglycaemia) and presence of sugar in the urine (glucosuria). Always use Valtropin as recommended by your doctor.
- If an allergic reaction to solvent occurs, the vials should be reconstituted with water for injections without preservative (metacresol) and used as a single use vial (see section 5 'How to store Valtropin'). **Do not use the supplied solvent if you have a known allergy to metacresol preservative**.

Monitoring during treatment by your doctor

- Valtropin may affect the way your body handles sugar from food and drink. Your doctor may check the amount of sugar in your urine or blood.
- Valtropin can affect the amount of thyroid hormone in the blood, so you must have thyroid function tests from time to time. If the thyroid is not working properly, Valtropin may not work as well as it should.

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Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Tell especially your doctor if you are taking
- adrenal steroid hormone such as cortisone or prednisolone
- insulin
- oral oestrogen
- sex hormones, medicines to treat stress response or inflammation (corticosteroids), medicines to treat epilepsy (e.g. carbamazepin)or cyclosporine (a medicine to suppress the immune system).

Your doctor may need to adjust the dose of Valtropin or of the other medicine.

Pregnancy
Valtropin should not be used during pregnancy unless clearly necessary. If you become pregnant, tell your doctor immediately.

Breast-feeding
If you are breast-feeding or intend to breast-feed, please ask your doctor for advice before using Valtropin.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines
Valtropin has no or negligible effect on the ability to drive and use machines.

Important information about some of the ingredients of Valtropin
The accompanying solvent of Valtropin contains metacresol. Do not use this solvent if you are allergic to metacresol (see section 2, **'**Do not use Valtropin'). If an allergic reaction to the solvent occurs, the vials should be reconstituted with water for injections and used as a single use vial (see section 5 'How to store Valtropin').

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3. HOW TO USE Valtropin

Always use Valtropin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Do not inject Valtropin yourself if you are not sure about the dose.

Dosage
Your doctor will tell you how much to use. This will vary according to your disease. Please do not change the dosage without consulting your doctor.

The accuracy of the Valtropin dose should be checked every 6 months by your doctor.

In general the dosage will be calculated as described below. However, individual doses may vary, and the doctor may change your dose based on your specific need.

Children

Growth hormone deficiency in children
Inject 0.025 - 0.035 milligrams (mg) for each kilogramme of body weight once daily under the skin (subcutaneously).

Children with Turner syndrome
Inject 0.045 - 0.050 milligrams (mg) for each kilogramme of body weight once daily under the skin (subcutaneously).

Children before puberty, who suffer from long-term kidney problems
Inject 0.045 - 0.050 milligrams (mg) for each kilogramme of body weight once daily under the skin (subcutaneously).

Adults

Growth hormone deficiency in adults
Inject 0.15 - 0.30 milligrams (mg) once daily under the skin (subcutaneously). A lower starting dose may be necessary if you are older or overweight.

If necessary, your doctor will gradually increase this dose according to your individual requirements based on the clinical outcome and measurement of your blood levels of a so called "growth factor" (known as IGF-1). The total daily dose usually does not exceed 1 mg. IGF-1 concentrations need to be regularly measured and should be maintained below the upper limit of the normal range for your age and sex.

Your doctor will always prescribe the minimum effective dose to be used.

Dosage adjustment
In elderly patients a dose reduction may be necessary.

The dosage of somatropin should be reduced in cases of long lasting swelling (oedema) or severe abnormal sensation (paresthesia), in order to avoid the development of a rare side effect called carpal tunnel syndrome (hand numbness and pain).

Following use of the medicine for some time, it may be necessary to reduce the dose, particularly in men.

When using other medicines the dose of Valtropin or of the other medicine may need to be adjusted (see section 2, 'Using other medicines').

Administration
Valtropin is intended for subcutaneous use after reconstitution. This means that after reconstitution of the powder with the solvent provided the solution is injected with a short needle into the fatty tissue just under the skin.

If you are injecting this medicine yourself you will be instructed how to prepare and give the injection.

Do not inject Valtropin yourself unless you have received training.

Detailed instructions for subcutaneous administration are provided with this leaflet (see section 'Information on how to self-inject Valtropin' at the end of this leaflet).

If you use more Valtropin than you should
In case more Valtropin was used than recommended, please consult your doctor.

If you have used too much Valtropin, initially your blood sugar may decrease and become too low (hypoglycaemia) and subsequently increase and become too high (hyperglycaemia). If you have used too much Valtropin over a longer period, this may result in a greater than normal growth of ears, nose, lips, tongue and cheekbone (acromegaly).

If you forget to use Valtropin
Do not take a double dose to make up for forgotten doses. Continue with the prescribed dosage regimen. If you have any doubts, please contact your doctor.

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If you stop using Valtropin
Please ask your doctor for advice before stopping treatment. Interruption or early stopping of treatment with Valtropin may impair the success of the growth hormone therapy.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valtropin can cause side effects, although not everybody gets them.

The side effects of medicines are classified as follows:

very common	affects more than 1 user in 10
common	affects 1 to 10 users in 100
uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000
not known	Frequency cannot be estimated from the available data

You may experience any of the following side effects after administration of Valtropin:

Very common	Headache in adults
	Abnormal sensation, such as pricking, tingling, or itchiness (paresthesia) in adults
	Joint pain (arthralgia) in adults
	Tissue swelling caused by accumulation of fluid in tissue (oedema) in adults
Common	Development of proteins that bind other substances (antibody building)
	Underactive thyroid gland (hypothyroidism)
	Impaired ability to reduce sugar levels (glucose tolerance)
	Mild increase of blood sugar levels (mild hyperglycaemia) (1% in children; 1% - 10% in adults)
	Abnormal increase of muscle tone (hypertonia)
	Sleeplessness (insomnia) in adults
	Increased blood pressure (hypertension) in adults
	Shortness of breath (dyspnoea) in adults
	Temporary interruption of breathing during sleep (sleep apnoea) in adults
	Numbness and tingling in fingers and palm of the hand due to squeezed nerve at hand wrist (carpal tunnel syndrome) in adults
	Joint pain (arthralgia) in children
	Muscle pain (myalgia)
	Tissue swelling caused by accumulation of fluid in tissue (oedema) in children
	Injection site reactions, weakness (asthenia)
Uncommon	Increased growth of new tissue (cancer, neoplasm)
	Lack of red blood cells (anaemia)
	Too little sugar in the blood (hypoglycaemia),
	Blood phosphate level above normal (hyperphosphatemia)

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	Personality disorder
	Rapid uncontrollable movement of the eyes (nystagmus)
	Swelling of the optic nerve head (papilloedema)
	Double vision (diplopia)
	Dizziness (vertigo)
	Accelerated heart beat (tachycardia)
	Vomiting
	Stomach pain (abdominal pain), wind (flatulence)
	Nausea
	Fat tissue decrease (lipodystrophy), thinning of the skin (skin atrophy), inflammation and peeling of skin (exfoliative dermatitis), swelling similar to after insect stings (urticaria), increased growth of male type hair on a woman's body (hirsutism), thickening of skin tissue (skin hypertrophy)
	Decrease in the muscle mass (muscle atrophy), bone pain
	Numbness and tingling in fingers and palm of the hand due to squeezed nerve at hand wrist (carpal tunnel syndrome) in children
	Involuntary loss of urine (urinary incontinence), blood in the urine (haematuria), passing more urine than normal (polyuria, pollakiuria), abnormal urine
	Genital discharge
	Enlargement of the male breast gland (gynaecomastia) in adults
	Injection site reactions like thinning of skin tissue, a copious discharge of blood from the blood vessels, thickening
	Weakness in children
Rare	Sugar disease (diabetes mellitus)
	Nerve disorder outside the brain and spinal cord (neuropathy), increased pressure in the skull (intracranial pressure increased)
	High blood pressure in the skull (benign intracranial hypertension)
	Abnormal sensation of the skin, such as pricking, tingling and itchiness (paresthesia) in children
	Increased blood pressure (hypertension) in children
	Diarrhoea
	Abnormal results in kidney function tests
Very rare	Sleeplessness (insomnia) in children
	Enlargement of the male breast gland (gynaecomastia) in children
Frequency not known	Single case of acute allergic reaction involving itching and swelling similar to insect stings and itching
	Severe reduction of insulin effects (insulin resistance)

In patients with adult-onset growth hormone deficiency swelling, muscle pain, joint pain and disorders have been reported early in therapy with somatropin but these effects tended to be transient (short-lived).

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If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE Valtropin

- Keep out of the reach and sight of children.
- Do not use Valtropin after the expiry date which is stated on the labels and the carton after EXP. The expiry date refers to the last day of that month.

Storage conditions of the unopened medicine
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- The non-reconstituted medicine can be kept at room temperature (not above 25°C) for one single period of up to 4 weeks before use.

Shelf-life after reconstitution with solvent
- After reconstitution with the solvent provided the medicine may be stored in the refrigerator (2°C - 8°C) for a maximum of 21 days.

Shelf-life after reconstitution with water for injections (NOT tap water)
- After reconstitution with water for injections the medicine must be used immediately and as a single use vial.

Do not use Valtropin if you notice that the solvent or the reconstituted solution is cloudy or discoloured or if contains particulate matters.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines that are no longer required. These measures will help to protect the environment.

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6. FURTHER INFORMATION

What Valtropin contains

Powder:
- The active substance is somatropin. One vial of powder contains 5 mg somatropin (corresponding to 15 IU). After reconstitution with 1.5 ml solvent, 1 ml contains 3.33 mg somatropin (corresponding to 10 IU).
- The other ingredients are glycine, mannitol, sodium phosphate monobasic, sodium phosphate dibasic and for pH (acidity) adjustment sodium hydroxide and hydrochloric acid.

Solvent:
- The pre-filled syringe contains water for injections and metacresol (see section 2, 'Important information about some of the ingredients of Valtropin').

What Valtropin looks like and contents of the pack

Valtropin is presented as a powder and solvent for solution for injection.

One pack contains:
- 5 mg of white to almost white powder in a glass vial closed with a rubber stopper and a cap
- 1.5 ml of solvent in a pre-filled syringe closed with a tip cap, for reconstitution as a clear solution.

Marketing Authorisation Holder and Manufacturer

BioPartners GmbH
Kaiserpassage 11
D-72764 Reutlingen
Germany
Tel: +49 (0) 7121 948 7756
Fax: +49 (0) 7121 346 255

This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

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INFORMATION ON HOW TO SELF-INJECT Valtropin

Please read the following instructions carefully before using Valtropin.

Introduction
The following instructions explain how to inject Valtropin yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject Valtropin. Do not attempt to inject yourself unless you are sure you understand the procedure and requirements of self-injection.

General notes
For patients with a known allergy to metacresol, Valtropin should not be reconstituted with the supplied solvent (see section 2, 'Do not use Valtropin'). If allergy to the accompanying solvent occurs, the vials should be reconstituted with water for injections: please fill a syringe with 1.5 ml of water for injections and follow the same instructions as for the pre-filled syringe (see section 5 'How to store Valtropin'). Do not use tap water.

Collect the necessary items before you begin. These are:

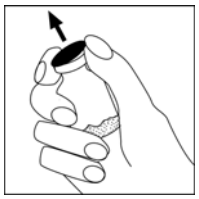
Supplied in the pack
- the Valtropin vial with powder for solution for injection
- the pre-filled syringe with 1.5 ml solvent for solution for injection

NOT supplied in the pack
- sterile injection syringe and needles
- alcohol swabs
- dry gauze or cotton pad
- an adhesive plaster
- disposal box for used syringes and needles.

Preparing the solution

1. Wash your hands thoroughly with soap and water before preparing the medicine.
2. Take the Valtropin carton out of the **refrigerator** and take the **powder vial** and **pre-filled syringe** with solvent out of the box. Check that the medicine is within the expiry date.

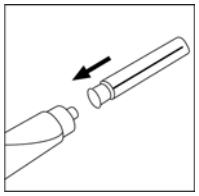
3. Remove the protective plastic cap from the powder vial.



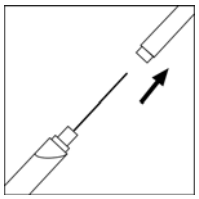
4. Clean the rubber stopper on the top of the powder vial with an alcohol swab. After cleaning do not touch the top of the vial.

Vial containing the powder of your medicine

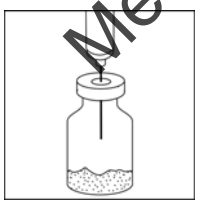
5. Take the **pre-filled syringe** with solvent supplied in the pack to prepare your medicine. Remove the rubber tip cap and firmly attach a needle to the syringe. Your doctor or his/her assistant will tell you what size of needle to use.



6. Remove the needle guard without touching the needle.



7. Slowly insert the needle straight through the centre of the rubber stopper of the vial.



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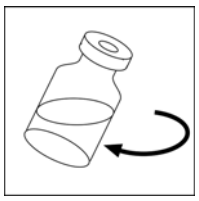
8. Slowly inject all of the solvent (1.5 ml) into the powder vial aiming the stream of liquid against the side of the vial. **DO NOT** aim it at the white powder at the bottom of the vial.

Before taking the syringe out of the vial, draw in the same amount of air (1.5 ml) as the solvent you injected to reduce the pressure in the vial. Withdraw the syringe and replace the needle guard.

9. Swirl the vial **GENTLY** to completely dissolve the contents. **DO NOT SHAKE.**



Dissolving up your medicine

10. The resulting solution should be clear, without particles.

11. Label the vial with the date on which you prepared the solution.

Preparing the injection

12. Clean the rubber stopper on the top of the vial with an alcohol swab again. After cleaning do not touch the top of the vial.

Vial containing the solution of your medicine

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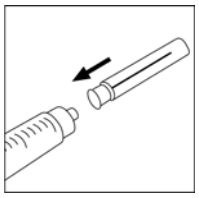
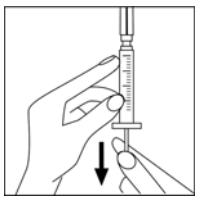
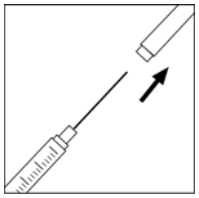
13. Take the **injection syringe** and the needle supplied by your pharmacy or hospital, to withdraw the solution of medicine. Remove the injection syringe from its sterile packaging and attach the needle to the syringe.



14. Fill the syringe with air by pulling the plunger back to the level that represents your dose as prescribed by your doctor.



15. Remove the needle guard without touching the needle.



16. Slowly insert the needle straight through the centre of the rubber stopper of the vial.

17. Gently push the plunger to discharge the air in the syringe into the vial.

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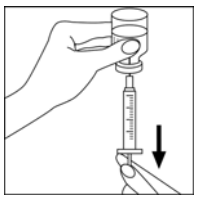
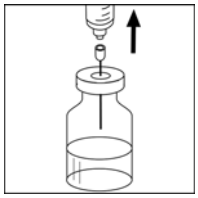
18. Turn the vial upside down with the needle still in it and hold the vial in one hand. Hold the syringe with the needle in the vial pointing up. Ensure that the tip of the needle is in the solution. Using your other hand slowly pull back the plunger in a continuous motion to draw the correct dose into the syringe ensuring that the needle tip remains in the solution.

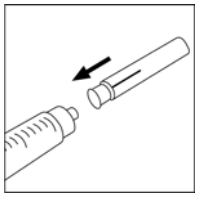


Withdrawing the right volume of your medicine with the help of the syringe markings

19. Remove the syringe from the needle leaving the needle in the vial without touching the tip of the syringe. Withdraw the needle, replace the needle guard and dispose in a closed container. For handling the vial see 'Injecting the solution', step 32.

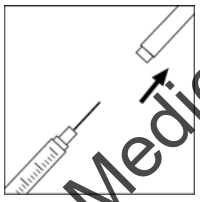


20. Take a new needle (one that is suitable for subcutaneous injection) and place it firmly onto the tip of the syringe.



Syringe containing your medicine being attached to a new needle

21. Remove the needle guard from the syringe needle and check for air bubbles in the syringe.



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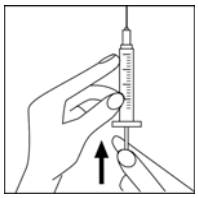
22. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing up, until the bubbles disappear. Push the plunger slowly back up to the correct dose.



23. Replace the needle guard and place the syringe with the needle on a flat surface.

Injecting the solution

24. Ensure the solution is at room temperature. If the solution is cold, warm the syringe between your palms.
25. Inspect the solution prior to administration: if the solution is discoloured or if you can see any solid particles in the liquid the solution **MUST NOT** be injected.
26. Select the injection site according to the recommendation of your doctor. It is very important that you **vary the injection site** each time you give the medicine.
27. Cleanse the injection site with an alcohol swab and wait for the area to dry.
28. Check that the correct dose of Valtropin solution is in the syringe. Hold the syringe in your hand as you would hold a pencil.
29. Squeeze a big skin fold between your thumb and index finger. Insert the needle into the pinched skin at a 45° to 90° angle with a quick, firm motion. This hurts less than pushing the needle in slowly.
30. Slowly (over a few seconds) inject the solution by gently depressing the plunger until the syringe is empty.
31. Withdraw the needle quickly and apply pressure over the injection site with a dry gauze or cotton pad for several seconds. If there is bleeding, cover the injection site with an adhesive plaster.
32. Dispose the used syringe in a closed container. Be sure to **return the vial to the refrigerator**. When empty, discard the vial as well. For shelf-life after reconstitution see section 5 'How to store Valtropin'.
    If the powder is reconstituted with water for injections, then the vial is for single use only. Any unused solution should be discarded.

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