SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Varitect® CP 25 IU/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human varicella-zoster immunoglobulin

Human plasma protein 50 mg/ml (of which at least 96 % is immunoglobulin G), with a content of antibodies against varicella-zoster virus of 25 IU/ml

The distribution of IgG subclasses is defined around 62 % IgG1, 33 % IgG2, 3 % IgG3, 2 % IgG4.

The immunoglobulin A (IgA) content is limited to ≤ 2 mg/ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Solution is clear or slightly opalescent and transparent to pale yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of varicella after exposure for:
- Children with negative history of varicella who are receiving immunosuppressive, cytostatic or radiotherapy or suffer from hereditary immunodeficiencies;
- Immunocompromised adults who, after careful evaluation are believed susceptible and have had significant exposure;
- Newborns of mothers who develop chicken pox within 5 days before and 2 days after delivery;
- Premature infants whose mothers have negative histories of varicella, as long as they require hospital care;
- Premature infants of less than 28 weeks of gestation or with a birth weight of 1000 g or less, regardless of maternal varicella history;

Adjuvant therapy of severe or complicated varicella-Zoster in immunocompromised patients or newborns at risk of dissemination.

4.2 Posology and method of administration

Posology
Prevention of chicken pox:
1 ml (25 IU) per kg body weight. In repeated exposure, e.g. household contact, higher doses are preferable. For post-exposure prophylaxis, Varitect CP should be administered as soon as possible and not later than 96 h after exposure.

Treatment of Zoster infections:
1 ml - 2 ml (25 - 50 IU) per kg body weight, with additional applications depending on the course of clinical manifestations.

Method of administration

Varitect CP should be infused intravenously at an initial rate of 0.1 ml/kg BW/hr for 10 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 1 ml/kg BW/hr for the remainder of the infusion.

4.3 Contraindications

Hypersensitivity to the active ingredients or to any other components.
Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA.

4.4 Special warnings and precautions for use

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "4.2 Posology and method of administration" must be closely followed as the incidence of adverse events tends to increase with the rate of infusion. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently
- in case of high rate of infusion,
- in patients with hypo- or agammaglobulinemia with or without IgA deficiency,
- in patients who receive human immunoglobulin for the first time or, in rare cases, when the human immunoglobulin product is switched or when there has been a long interval since the previous infusion.

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies.
Rarely, human immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human immunoglobulin.

Potential complications can often be avoided by ensuring:
- that patients are not sensitive to human immunoglobulin
- that by first injecting the medicinal product will be administered slowly (0.1 ml/kg BW/hour),
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human immunoglobulin, patients switched from an alternative intravenous immunoglobulin product, or when there has been a long interval since the previous infusion, should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

There is clinical evidence of an association between intravenous immunoglobulin administration and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing intravenous immunoglobulin in obese patients and in patients with pre-existing risk factors for thrombotic events such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity.

Cases of acute renal failure have been reported in patients receiving intravenous immunoglobulin therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products, or age over 65.

In case of renal impairment, intravenous immunoglobulin discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed intravenous immunoglobulin products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of intravenous immunoglobulin products that do not contain sucrose may be considered. Varitect CP does not contain sucrose.

In patients at risk for acute renal failure or thromboembolic adverse reactions, intravenous immunoglobulin products should be administered at the minimum infusion-rate practicable.

In all patients, intravenous immunoglobulin administration requires:
- adequate hydration prior to the initiation of the infusion of intravenous immunoglobulin,
- monitoring of urine output,
- monitoring of serum creatinine levels,
- avoidance of concomitant use of loop diuretics.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect. In case of shock, standard medical treatment for shock therapy should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that Varitect CP is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines
Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of Varitect CP, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Interference with serological testing
After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin. reticulocyte count and haptoglobin.

4.6 Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The following frequency convention is used for description of the following adverse reactions:
Very common: ≥1/10; common: ≥1/100, to <1/10; uncommon: ≥1/1.000, <1/100; rare: ≥1/10.000, <1/1.000; very rare: <1/10.000, not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Undesirable effects**	**Frequency**
Blood and lymphatic system disorders	Reversible haemolytic anaemia/haemolysis	Not known
Nervous system disorders	Headache	uncommon
Gastrointestinal disorders	Vomiting, nausea	uncommon
Renal and urinary disorders	Increase in serum creatinine level and/or acute renal failure	not known
Skin and subcutaneous tissue disorders	Transient cutaneous reactions	rare
Musculosketal and connective tissue disorders	Arthralgia, mild low back pain	uncommon
Infections and infestations	Reversible aseptic meningitis	not known
Vascular disorders	Low blood pressure	uncommon
	Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses	very rare
General disorders and administration site conditions	Chills, fever	uncommon
Immune system disorders	Allergic reactions Hypersensitivity reactions with sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hyper-sensitivity to previous administration.	uncommon rare

For safety with respect to transmissible agents, see 4.4.

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients and patients with renal impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Specific immunoglobulins, ATC code: J06BB09.

Varitect CP is an immunoglobulin preparation from plasma of donors with a high antibody titer against the varicella-zoster virus. It has a distribution of IgG subclasses closely proportional to that in native human plasma.

5.2 Pharmacokinetic properties

Varitect CP is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid; after approximately 3-5 days an equilibrium is reached between the intra- and extravascular compartments.

Varitect CP has a half-life of 23days. This half-life may vary from patient to patient and depends also on the clinical condition.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body.
In animals, single dose toxicity testing is of no relevance since higher doses result in overloading. Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.

Since clinical experience provides no hint for tumorigenic and mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

3 years.

The solution should be administered immediately after opening the receptacle. Any unused solution must be discarded because of bacterial contamination risk.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the container in the outer carton in order to protect from light.

Do not freeze.

The product should not be used after the expiry date indicated on the label.

6.5 Nature and contents of container

Ready-for-use solution for intravenous infusion in vials (type II glass) with a stopper (bromobutyl) and a cap (aluminium).

Infusion vial of 5 ml (125 IU)
Infusion vial of 20 ml (500 IU)
Infusion vial of 50 ml (1250 IU)

6.6 Special precautions for disposal and other handling

The medicinal product should be warmed to room or body temperature before use.

Dissolved products should be inspected visually for particular matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or which have deposits.

Any unused 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

November 2012