Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Varitect 25 IU/ml.
Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human varicella zoster immunoglobulin

1ml solution contains:

Active substance(s):

Human plasma protein	100	mg
Thereof immunoglobulin	=95	%
With antibodies to varicella zoster virus	25	I.U.

1gG subclass distribution:

1gG1	approx.	62.0%
1gG2	approx.	34.0%
1gG3	approx.	0.5%
1gG4	approx.	3.5%

1gA content =5mg
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indications for use

1. Prevention of varicella (chicken pox) for:

(a) Children with leukaemia, lymphoma, an immune deficiency or under treatment which weakens the immune response (immunosuppression, long-term treatment with adrenocortical hormones, radiotherapy).

(b) Neonates whose mothers contracted chicken pox within 5 days before the birth or shortly afterwards. Time of application: immediately after birth or when the first symptoms appear in the mother.

(c) Children suffering from other infectious disease during suspected infection with chicken pox.

(d) Pregnant women after suspected infection with the pathogens of chicken pox/zoster, who have not had chicken pox.

2. Treatment of zoster infections in high-risk patients, such as after radiation exposure or treatment with adrenocortical hormones or cytostatic drugs etc.

4.2 Posology and method of administration

Posology
Prevention of chicken pox: 0.2ml – 1 ml (5 - 25 I.U.) per kg body weight. In repeated exposure, e.g. household contact, higher doses are preferable. For post-exposure prophylaxis, Varitect should be administered as soon as possible and not later than 96 h after exposure.

Treatment of zoster infection: 1 ml – 2 ml (25 – 50 I.U.) per kg body weight, with additional applications depending on the course of clinical manifestations.

Method of administration
Varitect is intended for intravenous use. During the infusion, the rate of 20 drops per minute (corresponding to 1 ml per minute) must not be exceeded.

4.3 Contraindications

Hypersensitivity to any of the 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 "section 4.2, Posology and method of administration" must be closely followed. 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 agammaglobulinaemia with or without IgaA 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 by first injecting the product slowly (0.1 ml/kg/h),
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human immunoglbulin, patients switched from the alternative intravenous immunoglobulin (IVIg) product or when there has been a long interval since the previous 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 IVIg 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 immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg 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 immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity).

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

In case of renal impairment, IVIg 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 IVIg products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered. Varitect® does not contain sucrose.

In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at theminimum rate of infusion and dose practicable.

In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the infusion of IVIg,
- monitoring of urine output,
- monitoring of serum craetinine levels,
- avoidance of cocncomitant use of loop diuretics.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatments required depend on the nature and severity of the side effect.
In case of shock, standard medical treatment for shock 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. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulis 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® is andmnistered 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 this product, 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 patients 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.

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, 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

There are no indications that Varitect may impair the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely, immunglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no sensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Thrombotic events have been reported in the elderly, in patients with signs of cerebral or cardiac ischemia, and in overweight and severely hypovolaemic patients.

For information on viral safety see section 4.4, Special warnings and precautions for use.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Human varicella zoster immunoglobulin for intravenous administration.
ATC code: J06BB

Varitect is an immunoglobulin preparation from the plasma of donors who possess a high antibody titer against varicella zoster virus.

5.2 Pharmacokinetic properties

Varitect is immediately and completely bioavailable in the recipients circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravescular fluid; after approximately 3-5 days an equilibrium is reached between the intra-and extra-vascular compartments.
Varitect has a half-life of about 3 weeks. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

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 the 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 tumorogenic or mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.
Varitect is miscible with physiological saline solution. However, no other preparations may be added to the Varitect solution as any change in the electrolyte concentration or the pH may result in precipitation or denaturization of the proteins.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

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

Varitect should be stored in the refrigerator at +2 to +8°C, protected from light.

Do not freeze.

The solution should be administered immediately after opening the bottle.

6.5 Nature and contents of container

Varitect is provided in 50ml glass infusion bottles.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or which have a deposit.

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

7 MARKETING AUTHORISATION HOLDER

Biotest Pharma GmbH
Landsteinerstrasse 5
D-63303 Dreieich
Germany

8 MARKETING AUTHORISATION NUMBER

PA0592/003/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 21 April 1995
Date of last renewal: 20 April 2005

10 DATE OF REVISION OF THE TEXT

September 2006