1.4.3 Package Insert

1 NAME OF THE MEDICINAL PRODUCT

Ig VENA 50 g/l solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IgIV).

1 ml of solution contains:
human normal immunoglobulin mg 50
human proteins 50 g/l of which IgG at least 95%.
IgG subclasses:
IgG_1 24.3 - 37.2 mg
IgG_2 12.4 - 22.1 mg
IgG_3 0.9 - 1.5 mg
IgG_4 0.1 - 0.5 mg
Maximum IgA content 0.05 mg

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in
Primary immunodeficiency syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome.

Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
Children with congenital AIDS and recurrent infections.

Immunomodulation
Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.
Guillain Barré syndrome.
Kawasaki disease.

Allogeneic bone marrow transplantation

4.2 Posology and method of administration

Posology

The dose and dosage regimen is dependent on the indication.
In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4-6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur.
The recommended starting dose is 0.4-0.8 g/kg followed by at least 0.2 g/kg every three weeks.

The dose required to achieve a trough level of 6 g/l is of the order of 0.2-0.8 g/kg/month.

The dosage interval when steady state has been reached varies from 2-4 weeks.
Trough levels should be measured in order to adjust the dose and dosage interval.

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections

The recommended dose is 0.2-0.4 g/kg every three to four weeks.

Idiopathic Thrombocytopenic Purpura

For the treatment of an acute episode, 0.8-1.0 g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day for three to seven days.
Experience in children is limited.

Kawasaki disease

1.6-2.0 g/kg should be administered in divided dose over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Allogeneic bone marrow transplantation

Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant.
For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The starting dose is normally 0.5 g/kg/week, starting seven days before transplantation and for up to three months after transplantation.
In case of persistent lack of antibody production, dosage of 0.5 g/kg/month is recommended until antibody level returns to normal.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injections
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 – 0.8 g/kg - thereafter: 0.2 – 0.8 g/kg	every 2 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 – 0.4 g/kg	every 3 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/l
Children with AIDS	0.2 – 0.4 g/kg	every 3 – 4 weeks
Immunomodulation:		
Idiopathic Thrombocytopenic Purpura	0.8 – 1 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2 – 5 days
Guillain Barré syndrome	0.4 g/kg/d	for 3 – 7 days
Kawasaki disease	1.6 – 2 g/kg or 2 g/kg	in several doses for 2 - 5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid
Allogeneic bone marrow transplantation: - treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg	every week from day –7 up to 3 months after transplantation
- persistent lack of antibody production	0.5 g/kg	every month until antibody levels return to normal

Method of administration

Ig VENA should be infused intravenously at an initial rate of 0.46 – 0.92 ml/kg/hr (10 - 20 drops per minute) for 20 - 30 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 1.85 ml/kg/hr (40 drops/minute) for the remainder of the infusion.

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 "4.2 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 IgA deficiency
- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal 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 very seldom cases of IgA deficiency with anti-IgA antibodies.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Potential complications can often be avoided by ensuring:

- that patients are not sensitive to human normal immunoglobulin by initially injecting the product slowly (rate of administration 0.46 – 0.92 ml/kg/hr);
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg 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 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 of 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 immobilisation, 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 nephrotoxic 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 stabiliser 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. In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

This medicinal product contains 100 g of maltose per liter as an excipient. The interference of maltose in blood glucose assays may result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycaemia and death. Also, cases of true hypoglycaemia may go untreated if the hypoglycaemic state is masked by falsely elevated glucose readings. For further details see section 4.5.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg
- 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 should be implemented.

There have been reports of noncardiogenic pulmonary edema [Transfusion-related Acute Lung Injury (TRALI)] in patients administered IVIG. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1-6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IVIG recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see Laboratory tests).

Laboratory tests
If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (See Special warnings and precautions for use).

Viral safety
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 Ig VENA 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 Interactions with other medicinal products and other forms of interactions

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.

Blood Glucose testing

Some types of blood glucose testing systems (for example, those based on the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase methods) falsely interpret the maltose (100 mg/ml) contained in Ig Vena as glucose. This may result in falsely elevated glucose readings during an infusion and for a period of about 15 hours after the end of the infusion and, consequently, in the inappropriate administration of insulin, resulting in life-threatening or even fatal hypoglycemia. Also, cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated glucose readings. Accordingly, when administering Ig Vena or other parenteral maltose- containing products, the measurement of blood glucose must be done with a glucose-specific method.

The product information of the blood glucose testing system, including that of the test strips, should be carefully reviewed to determine if the system is appropriate for use with maltose-containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

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 or use machines have been observed.

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 human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity 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.

Very rarely thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

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 or patients with renal impairment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration; ATC code: J06BA02.
Ig VENA contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.
Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

5.2 Pharmacokinetic properties
Ig VENA 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 equilibrium is reached between the intra- and extravascular compartments.
Human normal immunoglobulin has a half-life of about 21 days. 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. Moreover, as administration of immunoglobulins in animal studies may lead to the formation of antibodies, preclinical safety data are limited. However, the limited animal studies did not show special risks for humans, based on acute and sub-acute toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose
Water for injection.

6.2 Incompatibilities

Human normal immunoglobulin for intravenous use must not be mixed with other medicinal products.

6.3 Shelf-life

2 years.
Once the infusion container has been opened the contents should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Keep the vial in the outer carton.
Do not freeze.

6.5 Nature and contents of container

20 ml solution in a vial (Type I glass) with a stopper (halobutyl Type I rubber); pack size of one vial.
50 ml, 100 ml and 200 ml solution in a vial (Type I glass) with a stopper (halobutyl Type I rubber): pack size of one vial + infusion set.

6.6 Instructions for use and handling and disposal

The product should be brought to room or body temperature before use.
The solution should be clear or slightly opalescent.
Do not use solutions that are cloudy or have deposits.
Solution should be inspected visually for particulate matter and discoloration prior to administration.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 DATE OF REVISION OF THE TEXT

2 Oct 2011