Ig VENA 50 g/l Solution for infusion
Human normal immunoglobulin (IVIg) for intravenous use

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:
1. What Ig VENA is and what it is used for
2. What you need to know before you use Ig VENA
3. How to use Ig VENA
4. Possible side effects
5. How to store Ig VENA
6. Contents of the pack and other information

1. What Ig VENA is and what it is used for
Ig VENA is a solution of human normal immunoglobulin for intravenous use. Immunoglobulins are human antibodies present also in the blood. Ig VENA is used for:

Treatment of adults, and children and adolescents (0-18 years) who do not have sufficient antibodies (replacement therapy) in the following cases:
1. Patients with inborn deficiency of antibodies production (primary immunodeficiency syndromes)
2. Patients with disease (cancer) of the blood (chronic lymphocytic leukaemia) that lead to a reduced antibody production (hypogammaglobulinaemia) and recurrent bacterial infections, when prophylactic antibiotics have failed.
3. Patients with cancer of the bone marrow (multiple myeloma) that leads to a reduced antibody production (hypogammaglobulinaemia), with recurrent bacterial infections, who have failed to respond to the vaccine against the bacteria pneumococci.
4. Patients with reduced antibody production (hypogammaglobulinaemia) after an allogeneic haematopoietic stem cell transplantation HSCT (that it does not come from the same person).

Treatment of adults, and children and adolescents (0-18 years) with certain inflammatory disorders (immunomodulation) in the following situations:
1. Patients who do not have enough blood platelets (Primary Immune Thrombocytopenia, ITP), and who are at high risk of bleeding or prior to surgery to correct of platelets count.
2. Patients with Guillain Barré syndrome. This is an acute disease that is characterised by inflammation of the peripheral nerves that causes severe muscle weakness mainly in the legs and upper limbs.

3. Patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). This chronic disease is a rare disorder of the peripheral nerves characterized by gradually increasing weakness of the legs and, to a lesser extent, the arms.

4. Patients with Kawasaki disease. This is an acute disease of primarily young children characterised by an inflammation of the blood vessels throughout the body.

2. What you need to know before you use Ig VENA

Do not use Ig VENA

- If you are allergic (hypersensitive) to human immunoglobulins or any of the other ingredients of this medicine (listed in section 6).
- If you have antibodies against immunoglobulins IgA in your blood. This is very rare and may occur if you do not have immunoglobulins of the type IgA in your blood.

Warnings and precautions

Talk to your doctor or nurse before using Ig VENA.

Your doctor or health care professional will closely follow you and carefully observe you throughout the infusion period with Ig VENA to make sure that you do not suffer reactions.

Certain adverse reactions may occur more frequently:
- in case of high rate of infusion;
- if you suffer from a condition with low antibody levels in your blood (hypo- or agammaglobulinaemia, with or without IgA deficiency);
- if you receive human normal immunoglobulin for the first time;
- in rare cases when the human normal immunoglobulin product is changed, or when there has been a long interval from the previous infusion.

- In certain conditions, immunoglobulins may increase the risk of cardiac infarction, stroke, lung embolism, or deep vein thrombosis, as they increase blood viscosity.

Therefore, your doctor will take special care in the following circumstances:
- you are overweight,
- you are elderly,
- you have diabetes,
- you suffer from high blood pressure (hypertension),
- your blood volume is too low (hypovolaemia),
- you have or already had problems with your blood vessels (vascular diseases),
- you suffer from an increased tendency for blood clotting (hereditary or acquired thrombotic disorders),
- you suffer from thrombotic episodes,
- you suffer from a disease which causes your blood to thicken (viscosity),
- you have been bedridden for a long time,
- you have or had problems with your kidneys or if you are taking medicines that can damage your kidneys (nephrotoxic medicines), as cases of acute kidney failure were reported. In the case of kidney disorder, your doctor will consider treatment interruption.

- You may be allergic (hypersensitive) to immunoglobulins (antibodies) without knowing it.

This may occur even if you have previously received human normal immunoglobulins and had tolerated them well. It may happen particularly if you do not have immunoglobulins of
the type IgA (IgA deficiency with anti-IgA antibodies). In these rare cases allergic reactions (hypersensitive) such as a sudden fall in blood pressure or shock may occur.

In case of adverse reaction, your doctor may decide either to reduce the rate of administration or to stop the infusion. Furthermore your doctor will decide the treatment required depending on the nature and severity of the side effect.

In case of shock, standard medical treatment for shock should be implemented. Please tell your doctor if at least one of the above conditions applies to you, your doctor will take particular care in prescribing and administering Ig VENA to you.

**Viral safety**
Medicines made from human blood or plasma, are submitted to a certain number of safety measures to prevent infections being passed on to patients. These include careful selection of blood or plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus. Manufacturers of these medicinal products also include steps in the processing of the blood or plasma that can inactivate or remove the pathogens. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections this may be due to the fact that the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of Ig VENA the name and batch number of the product are recorded in order to maintain a record of the batches used.

**Children and adolescents**
No specific measures or monitoring are required.

**Other medicines and Ig VENA**
Tell your doctor if you are taking, have recently taken or might take any other medicines. Human normal immunoglobulin for intravenous use must not be mixed with other medicinal products.

**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 medicinal product an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, the impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

**Blood test**
Ig VENA may interfere with some blood tests due to the transitory rise of the various passively transferred antibodies in your blood after injection of immunoglobulin; this antibodies rise may result in misleading results in serological testing. Passive transmission of antibodies to erythrocyte
antigens, e.g. A, B, D (which determine the blood group), may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs’ test).

**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.

**Children and adolescents**

Although specific interaction studies have not been performed in the paediatric population, no differences between adults and children are to be expected.

**Pregnancy, breast-feeding and fertility**

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will decide if Ig VENA may be used during pregnancy and breast-feeding.
- No clinical trials have been made with Ig VENA in pregnant women. IVIg products have been shown to cross the placenta, increasingly during the third trimester. However, medicines that contain antibodies have been used in pregnant women for years, and it has been shown that there are no harmful effects on the course of pregnancy, or on the foetus and the neonate to be expected.
- If you are breast-feeding and receive Ig VENA, the antibodies of the medicine may pass in the breast milk. Therefore, your baby may be protected from certain infections.
- Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

**Driving and using machines**

The ability to drive and operate machines may be impaired by some adverse reactions associated with Ig VENA. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

**Ig VENA contains maltose and sodium**

The product contains 100 mg maltose per ml.

This medicinal product contains 69 mg sodium per liter. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Ig VENA
Ig VENA can be administered only in hospitals or health care facilities by doctors or health care professionals. Dosage and treatment scheme depend on the indication; the doctor will establish the dose and treatment appropriate for you. At the beginning of the infusion you will receive Ig VENA at a slow infusion rate. If you tolerate this well your doctor can gradually increase the infusion rate.

**Use in children and adolescents**
The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the patient.

**If you use more Ig VENA than you should**
If you get more Ig VENA than you should, a fluid protein overload may occur and the blood can become too thick (hyperviscosity); it could particularly happen when you are a patient at risk, particularly in elderly patients or in patients with cardiac or renal impairment.

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

**4. Possible side effects**
Like all medicines, this medicine can cause side effects, although not everybody gets them.

- Occasionally adverse reactions may occur such as: chills, headache, dizziness, fever, vomiting, nausea, allergic reactions, arthralgia (articulation pains), low blood pressure and moderate low back pain.
- Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, hypersensitivity reactions (anaphylactic shock), even when the patient has shown no hypersensitivity to previous administration.
- Cases of transitory non-infective meningitis (reversible aseptic meningitis), isolated cases of temporary red blood cells reduction (reversible haemolytic anaemia/haemolysis) and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin infusions.
- Increase in serum creatinine level in blood and/or acute renal failure have been observed.
- Very rarely thromboembolic events (formation of blood clots) that may cause myocardial infarction, stroke, obstruction of the pulmonary veins (pulmonary embolism) and deep vein thromboses have been reported.

During Clinical Trial KB034, in which 756 doses of Ig VENA were administered to 33 adult subjects affected by CIDP, one patient experienced once headache.

**Additional side effects in children and adolescents**
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

For information on viral safety see section 2 “Before you use Ig VENA”.

**Reporting of side effects**
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ig VENA
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and on the outer carton after “EXP”. The expiry date refers to the last day of that month. Store in a refrigerator (2°C - 8°C).

Once the container for the infusion has been opened, the content should be used immediately. Keep the vial in the outer carton. Do not freeze.

Do not use this medicine if you notice that the solution is cloudy or contains deposits or has a change of colour.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Ig VENA contains
The active substance is human normal immunoglobulin.
1 ml of solution contains 50 mg of human normal immunoglobulin.

The solution contains 50 g/l of human proteins of which at least 95% of immunoglobulin G (IgG).

The IgG subclasses (IgG) have the following distribution:

| IgG1 | 62.1 % |
| IgG2 | 34.8 % |
| IgG3 | 2.5 % |
| IgG4 | 0.6 % |

The maximum IgA content is 50 micrograms/ml.

Produced from the plasma of human donors.
The other ingredients are maltose and water for injections.

What Ig VENA looks like and contents of the pack
Ig VENA is a solution for infusion, clear or slightly opalescent, colourless or pale yellow.

Ig VENA 1 g/20 ml solution for infusion, 20 ml vial

Marketing Authorisation Holder and manufacturer
Marketing authorisation holder:
Kedrion S.p.A. - Loc. Ai Conti, 55051 Castelvecchio Pascoli, Barga (Lucca), ITALY.

Manufacturer: Kedrion S.p.A., 55027 Bolognana, Gallicano (Lucca), ITALY.

This medicinal product is authorised in the Member States of the EEA under the following names:

<table>
<thead>
<tr>
<th>Country</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Ig Vena 50 g/l Infusionslösung</td>
</tr>
<tr>
<td>Germany</td>
<td>Ig Vena 50 g/l Infusionslösung</td>
</tr>
</tbody>
</table>
The following information is intended for medical or healthcare professionals only:

Instructions for a correct use

- Ig VENA should be warmed to room or body temperature before administration.
- Before administration solution should be inspected visually for particulate matter and changes in colour prior to administration. Solutions that are cloudy or have deposits should not be used.
- 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).

Special precautions

Some severe adverse reactions to the product may be due to the infusion rate. 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 naïve 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.

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.

Children and adolescents

No specific measures or monitoring are required for the paediatric population. No difference is expected in the paediatric population (0-18 years).

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which are 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).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

**Acute renal failure**
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 containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products not containing such excipients may be considered. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

**Aseptic meningitis syndrome (AMS)**
Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm³, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.
AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

**Haemolytic anaemia**
IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs’ test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis.

This medicinal product contains 100 mg of maltose per ml 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 paragraph “Blood Glucose Testing”.

**Dosage Recommendations**
Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.
Posology
The dose and dose regimen is dependent on the indication. In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes
The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 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 given once, followed by at least 0.2 g/kg given every three to four weeks. The dose required to achieve a trough level of 5-6 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 3 - 4 weeks.
Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels.

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections
The recommended dose is 0.2 - 0.4 g/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation
The recommended dose is 0.2-0.4 g/kg every three to four weeks. The trough levels should be maintained above 5 g/l.

Primary immune thrombocytopenia
There are two alternative treatment schedules:
- 0.8 – 1 g/kg on day one; this dose may be repeated once within 3 days;
- 0.4 g/kg given daily for two to five days.
The treatment can be repeated if relapse occurs.

Guillain Barré syndrome
0.4 g/kg/day over 5 days.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
Initial dose: 2 g/kg in 4 consecutive days; it is recommended to administrate the initial dose every 3-4 weeks until the maximum benefit is achieved.
Maintenance dose: to be defined by the treating physician; it is recommended that once the maximum benefit is achieved, the dose is reduced and administration frequency adjusted until the lowest effective maintenance dose is identified.
The initial dose has been shown to be well tolerated for up to 7 consecutive treatment cycles carried out over a period of 6 months

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

The dosage recommendations are summarised in the following table:

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<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency of injections</th>
</tr>
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<tbody>
<tr>
<td>Replacement therapy in primary immunodeficiency</td>
<td>starting dose: 0.4 – 0.8 g/kg</td>
<td>every 3 – 4 weeks to obtain IgG trough level of at least 5 – 6 g/l</td>
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<tr>
<td></td>
<td>thereafter: 0.2 – 0.8 g/kg</td>
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<tr>
<td>Replacement therapy in secondary immunodeficiency</td>
<td>0.2 – 0.4 g/kg</td>
<td>every 3 – 4 weeks to obtain IgG trough level of at least 5 – 6 g/l</td>
</tr>
<tr>
<td>Congenital AIDS</td>
<td>0.2 – 0.4 g/kg</td>
<td>every 3 – 4 weeks</td>
</tr>
<tr>
<td>Hypogammaglobulinaemia (&lt; 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation</td>
<td>0.2 – 0.4 g/kg</td>
<td>every 3 - 4 weeks to obtain IgG trough level above 5 g/l.</td>
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<tr>
<td>Immunomodulation:</td>
<td></td>
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<tr>
<td>Primary immune thrombocytopenia</td>
<td>0.8 – 1 g/kg or 0.4 g/kg/d</td>
<td>on day 1, possibly repeated once within 3 days</td>
</tr>
<tr>
<td>Guillain Barré syndrome</td>
<td>0.4 g/kg/d</td>
<td>for 2 – 5 days</td>
</tr>
<tr>
<td>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)*</td>
<td>- starting dose: 2 g/Kg</td>
<td>in 4 consecutive days every 3-4 weeks</td>
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<td></td>
<td>- thereafter: Maintenance dose</td>
<td>to be adjusted to patient’s needs, see above</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>1.6 – 2 g/kg or 2 g/kg</td>
<td>in divided doses over 2 - 5 days in association with acetylsalicylic acid</td>
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<tr>
<td></td>
<td></td>
<td>in one dose in association with acetylsalicylic acid</td>
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</table>

*The dose is based on the dose used in the clinical study conducted with Ig VENA

**Special populations**
Experience in subjects aged 65 and over is limited.

**Use in children and adolescents**
The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

**CIDP**

Due to the rarity of the disease and consequently the overall low number of patients, only limited experience is available of use of intravenous immunoglobulins in children with CIDP; therefore, only data from literature are available. However, published data are all consistent in showing that the IVIg treatment is equally effective in adults and children, as it is the case for the IVIg established indications.