1 NAME OF THE MEDICINAL PRODUCT

Ig VENA

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg).

Solution for intravenous (IV) infusion.

One ml of solution contains:
Human normal immunoglobulin 50 mg
(purity of at least 95% IgG)

Each vial of 20 ml contains: 1 g of human normal immunoglobulin
Each vial of 50 ml contains: 2.5 g of human normal immunoglobulin
Each vial of 100 ml contains: 5 g of human normal immunoglobulin
Each vial of 200 ml contains:10 g of human normal immunoglobulin

The maximum IgA content is 50 micrograms/ml.

Produced from the plasma of human donors.

Excipients with known effect:
The product contains 100 mg of maltose per ml.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
The solution should be clear or slightly opalescent, colourless or pale yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l

* PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, and children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré syndrome
- Kawasaki disease (in conjunction with acetylsalicylic acid; see 4.2)
- Chronic inflammatory demyelinating poliradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

4.2 Posology and method of administration

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.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.

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 6 g/L or within the normal reference range for the population age. Three to six months are required after the initiation of therapy for equilibration (steady-state IgG levels) 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 IgG 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.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Secondary immunodeficiencies (as defined in 4.1.)
The recommended dose is 0.2-0.4 g/kg every three to four weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

Primary immune thrombocytopenia

There are two alternative treatment schedules:
- 0.8-1 g/kg given 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 (possible repeat of dosing in case of relapse).

Kawasaki disease
2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Chronic inflammatory demyelinating polyneuropathy (CIDP)
Starting dose: 2 g/kg in 2-5 consecutive days
Maintenance doses:
1 g/kg over 1-2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal Motor Neuropathy (MMN)
Starting dose: 2 g/kg given over 2-5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.
The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of injections**
Replacement therapy		
Primary immunodeficiency syndromes	Starting dose: 0.4 - 0.8 g/kg Maintenance dose: 0.2- 0.8 g/kg	every 3 - 4 weeks
Secondary Immunodeficiencies (as defined in 4.1.)	0.2 - 0.4 g/kg	every 3 - 4 weeks
Immunomodulation:		

Primary immune thrombocytopenia	0.8 -1 g/kg	on day 1, possibly repeated once within 3 days
	Or 0.4 g/kg/d	 for 2 - 5 days
Guillain Barré syndrome	0.4 g/kg/d	for 5 days
Kawasaki disease	2 g/kg	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2 g/kg Maintenance dose : 1 g/kg	 in divided doses over 2-5 days every 3 weeks over 1-2 days
Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg or 2 g/kg	 over 2-5 consecutive days every 2-4 weeks or every 4-8 weeks over 2-5 days

Paediatric population
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.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

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.

Method of administration

For intravenous use.

Human normal immunoglobulin 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. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the rate of administration may be gradually increased to a maximum of 1.85 ml/kg/hr (40 drops/minute).

In PID patients who tolerate the infusion rate of 0.92 ml/kg/hr, the rate of administration may be gradually increased to 2 ml/kg/hr, 4 ml/kg/hr, up to a maximum of 6 ml/kg/hr, every 20-30 minutes and only if the patient tolerates the infusion well.

In general, dosage and infusion rates have to be individually tailored according to the patient's needs. Depending on body weight, dosage and occurrence of adverse reactions, the patient may not reach the maximum infusion speed. In case of adverse reactions, the infusion should be immediately stopped and it should be resumed at the appropriate infusion rate for the patient.

See also paragraph 6.6

Special populations
In paediatric patients (0-18 years) and elderly (> 64 years of age), the initial rate of administration should be 0.46 – 0.92 ml/kg/hr (10 - 20 drops per minute) for 20 - 30 minutes. If well tolerated and considering patient’s clinical conditions, the rate may be gradually increased to a maximum of 1.85 ml/kg/hr (40 drops/minute).

4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients listed in section 6.1.
Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

4.4 Special warnings and precautions for use

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 section 4.5.* For acute renal failure see below.

This medicinal product contains approximately 3 mmol/liter (or 69 mg/liter) sodium. To be taken into consideration by patients on a controlled sodium diet.

Precautions for use
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);
- 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 at the hospital 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 (see 4.5).

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 adverse reaction.

Infusion reaction
Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) may be related to the rate of infusion. The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently:
- 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
- in patients with an untreated infection or underlying chronic inflammation

Hypersensitivity
Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients:
- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

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 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).

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.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While 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 that do not contain these excipients may be considered. Ig VENA contains maltose. (See section 6.1).

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment.
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 mm^3, 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.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

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. (See section 4.8.).

Neutropenia/Leukopenia
A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIgs. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)
In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing
After the administration 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 antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents
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, 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.

Paediatric population
Cases of glycosuria have been reported in paediatric patients after administration of Ig VENA. These events are usually mild and transient with no clinical signs.
Ig VENA contains 100 mg of maltose per ml as an excipient. In the renal tubules, maltose is

hydrolysed to glucose which is reabsorbed and generally very little is excreted in the urine. The glucose reabsorption is age dependent. The transitory increase of maltose in plasma may exceed the renal capacity of sugar re-absorption, and result in positive testing for glucose in the urine.

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 medicinal 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.

Loop diuretics
Avoidance of concomitant use of loop diuretics.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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. IVIg products have been shown to cross the placenta, increasingly during the third trimester.
Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are expected.

Breast-feeding
Immunoglobulins are excreted into human milk. No negative effects on the breastfed

newborns/infants are anticipated.

Fertility
Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use 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.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

The safety of Ig VENA was evaluated in four clinical trials in which a total of 1189 infusions was administered. The CIDP study enrolled 24 patients with Chronic Inflammatory Demyelinating Poliradiculoneuropathy (CIDP) receiving Ig VENA, for a total of 840 infusions administered. In the PID study, 16 patients with Primary Immunodeficiency (PID) were enrolled and received a total of 145 infusions. The ITP study enrolled 15 subjects with Immune Thrombocytopenia (ITP) with a total of 80 infusions administered. In the ID/ITP study, 43 patients with either Immunodeficiency (ID) or ITP were enrolled and received a total of 124 infusions.

Tabulated list of adverse reactions
The tables presented below are according to the MedDRA system organ classification (SOC and Preferred Term Level).
Table 1 shows the adverse reactions from clinical trials and Table 2 shows the post-marketing adverse reactions.
Frequencies have been evaluated according to the following convention: 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).
Frequencies of undesirable effects from clinical trials are based on percentage per infusions (total

number of infusions: 1189).

Adverse reactions from post-marketing experience are listed with unknown frequency as post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size and it is not possible to reliably estimate the frequency of these reactions.

Source of the safety database (e.g. from clinical trials, post-authorisation safety studies and/or spontaneous reporting)

Table 1
Frequency of Adverse Reactions from Clinical Trials

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency per patient	Frequency per infusion
Nervous system disorders	Headache, somnolence	Common	Rare
Gastrointestinal disorders	Nausea	Common	Rare
Musculoskeletal and connective tissue disorders	Back pain	Common	Uncommon
	Myalgia	Common	Rare
General disorders and administration site conditions	Asthenia, fatigue, pyrexia	Common	Rare

Table 2
Post-marketing Adverse Reactions

MedDRA SOC	Adverse reaction	Frequency per patient	Frequency per infusion
Infections and infestations	Meningitis aseptic	Not known	Not known
Blood and lymphatic system disorders	Haemolysis, haemolytic anaemia	Not known	Not known
Immune system disorders	Anaphylactic shock, hypersensitivity	Not known	Not known
Psychiatric disorders	Confusional state	Not known	Not known
Nervous system disorders	Cerebrovascular accident, headache, dizziness, tremor, paraesthesia	Not known	Not known
Cardiac disorders	Myocardial infarction, cyanosis, tachycardia, bradycardia, palpitations	Not known	Not known
Vascular disorders	Deep vein thrombosis, embolism, hypotension, hypertension, pallor	Not known	Not known
Respiratory, thoracic and	Pulmonary embolism,	Not known	Not known

Table 2 **Post-marketing Adverse Reactions**			
MedDRA SOC	**Adverse reaction**	**Frequency per patient**	**Frequency per infusion**
mediastinal disorders	pulmonary oedema, bronchospasm, dyspnoea, cough		
Gastrointestinal disorders	Vomiting, diarrhoea, nausea, abdominal pain	Not known	Not known
Skin and subcutaneous tissue disorders	Angioedema, urticaria, erythema, dermatitis, rash, pruritus, eczema, hyperhidrosis	Not known	Not known
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, myalgia, neck pain, muscoloskeletal stiffness	Not known	Not known
Renal and urinary disorders	Acute kidney injury	Not known	Not known
General disorders and administration site conditions	Injection site phlebitis, pyrexia, chills, chest pain, face oedema, malaise	Not known	Not known
Investigations	Blood pressure decreased, blood creatinine increased	Not known	Not known

For safety with respect to transmissible agents, see section 4.4.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Transient glycosuria has been observed after administration of Ig VENA in paediatric patients.

This event could be due to the maltose contained in Ig VENA and to the different capacity of renal tubules to reabsorb glucose, that is an age dependent mechanism.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: *https://sideeffects.health.gov.il /*

Additionally, you should also report to Kamada Ltd. to email address:
pharmacovigilance@kamada.com

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including

elderly patients or patients with cardiac or renal impairment (see section 4.4.).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration; ATC code: J06BA02.
Human normal immunoglobulin 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.

Clinical efficacy and safety
Four clinical trials were performed with Ig VENA: three trials on efficacy and safety in patients with Primary Immunodeficiency (PID), Immune Thrombocytopenia (ITP) and Chronic Inflammatory Demyelinating Poliradiculoneuropathy (CIDP); and one study on safety and tolerance of Ig VENA at increased infusions rates in patients with Immunodeficiency (ID) or ITP.

A phase III, prospective, open-label study in patients with primary Immunodeficiency syndromes (KB028) evaluated the pharmacokinetic profile of Ig VENA as the primary objective. Secondary objectives were therapeutic efficacy in terms of prophylaxis of episodes of infection, and safety in terms of short term-tolerability. Fifteen patients out of 16 enrolled, aged 28-60 years old, were evaluated for efficacy and were treated for 24 weeks with Ig VENA (total of 140 infusions).
The pharmacokinetic profile of Ig VENA showed a terminal half-life fairly consistent with the data reported in the literature, being 26.4 days. One patient developed pneumonia after 18 weeks of therapy with Ig VENA but this patient suffered of severe pulmonary infections also in the previous 10 years. No serious infections were reported for the other patients enrolled.
The data generated in KB028 study indicate that Ig VENA is safe and effective for treatment of primary immunodeficiency syndromes.

The ITP Study (KB027) was a phase III, open-label, prospective trial for the evaluation of efficacy and tolerability of Ig VENA in adult patients with chronic idiopathic thrombocytopenic purpura. The primary objective was the evaluation of platelet count increase. Secondary objectives were: reduction in haemorrhagic events, duration of platelet response, and the incidence of AEs. Fifteen patients received a total dose of 2 g/kg each, subdivided into 5 daily infusions of 400 mg/kg on consecutive days. A second cycle of 2 g/kg body weight was given to one patient within the first 14 days. The total number of infusions applied was 80.
All enrolled patients achieved a platelet count $\geq 50x10^9$/L, except one who received a second cycle of therapy but did not achieve the target platelet count (response rate 93.3%, 90% CI from 68.1 to 99.8). No adverse events were reported.
The results obtained from KB027 study provided evidence of tolerability and therapeutic efficacy of Ig VENA in ITP patients.

In the phase III study KB057 for the evaluation of tolerability and safety of Ig VENA at increased infusion rates, 43 adult patients were enrolled: 38 ID and 5 ITP patients who received Ig VENA at the dosages approved according to both indications.

Thirty-seven ID patients were observed for 3 infusions and 1 ID patient for 2 infusions. Four ITP patients received their planned dose over 2 daily infusions, while 1 patient was infused over 3 days. (total of 124 infusions).

At infusion 2, twenty-eight patients out of 43 were infused at the maximum speed of 8 ml/kg/hr; 13 patients out of 43 reached only a maximum infusion speed of 6 ml/kg/hr, because their infusion was finished before they could be ramped up to the next increment in infusion speed. During the clinical trial, two patients did not reach 8 ml/kg/h because they developed 3 adverse events during the infusion at lower infusion rates.

Results obtained from this study show that Ig VENA administered at increasing infusion speed was well tolerated both in patients with ID and in those with ITP and that the infusion speed could be ramped up to a maximum of 6 ml/kg/hr and, in a limited number of patients, to 8 ml/kg/hr.

Adverse drug reactions were reported in less than 10% of ID patients and were reactions generally related with IVIg administration (e.g. pyrexia, back pain, myalgia, asthenia, somnolence and fatigue).

No serious ADR was reported as well as local reactions at the infusion site.

Clinical trial conducted with Ig VENA on patients with Chronic Inflammatory Demyelinating Poliradiculoneuropathy (CIDP):

The double-blind controlled Phase III study on the tolerability and efficacy of long-term treatment with high doses intravenous immunoglobulins versus high doses intravenous methylprednisolone (IVMP) in CIDP (KB034) was conducted of a total of 46 CIDP adult patients, randomised to receive either *Ig VENA* (dosage: 2 g/Kg/month in 4 consecutive days for 6 months) or IVMP (dosage: 2 g/month in 4 consecutive days for 6 months).

Ten of the 21 patients treated with IVMP (47.6%) completed the 6 months of the study compared to 21/24 on Ig Vena (87.5%) ($p = 0.0085$). The cumulative probability of treatment discontinuation was significantly higher with IVMP than with Ig VENA at 15 days, 2 months and 6 months. Of the 11 patients who discontinued IVMP, eight did so because of progressive worsening after treatment start (5 patients) or failure to improve after two courses of therapy (3 patients), while one had adverse events (gastritis) (9.1%) and two voluntarily withdrew (18.2%). Three patients discontinued Ig VENA for progressive worsening after starting the therapy (two patients), or absence of improvement after two courses of therapy (one patient). All the patients worsening or not improving after IVMP or IVIg were shifted to the alternative therapy while the three patients who discontinued IVMP for adverse event or who voluntary withdrew after IVMP refused further therapy.

Results regarding the study secondary endpoints are summarized in the table reported below (statistically significant differences in bold):

	Intention To Treat Population (ITT)			*Per Protocol Population (PP)*		
Secondary endpoints	**IgVENA 10 g/200 ml**	**MPIV**	**p-value**	**IgVENA 10 g/200 ml**	**MPIV**	**p-value**
Relapses rate *	45.8% (n 11/24)	52.4% (n 11/21)	0.7683	38.1% (n 8/21)	0% (n 0/10)	**0.0317**
MRC sum score [delta (p-value)]	+4.7 (**0.0078**)	+1.8 (0.1250)	0.6148	+4.0 (**0.0469**)	+2.0 (0.5000)	0.5473
INCAT (p-value)	**0.0004**	0.1877	0.3444	**0.0057**	0.2622	0.9065
Vibratory score - Right medial malleolus (p-value)	<0.0001	0.6515	**0.0380**	**0.0009**	0.2160	0.4051
Fist strength right [delta (p-value)]	+19.4 (**0.0005**)	+5.4 (0.6169)	0.0641	+16.5 (**0.0044**)	+14.7 (**0.0156**)	0.5012
Fist strength left [delta (p-value)]	+16.9 (**0.0011**)	+8.8 (0.1170)	0.1358	+12.7 (**0.0014**)	+10.5 (**0.0156**)	0.3330
Time on 10 meters [delta (p-value)]	-3.2 (**0.0025**)	-0.5 (0.2051)	0.0800	-3.5 (**0.0043**)	-2.0 (0.4453)	0.2899
ONLS scale (p-value)	**0.0006**	0.0876	0.4030	**0.0033**	0.0661	0.8884
Rankin scale (p-value)	**0.0006**	0.0220	0.3542	**0.0132**	0.2543	0.8360
Rotterdam scale [delta (p-value)]	+1.4 (**0.0071**)	+1.3 (**0.0342**)	0.6465	+1.1 (**0.0342**)	+1.1 (0.0859)	0.4056
SF-36 QoL	+14.2 (**0.0011**)	+16.7 (**0.0008**)	0.3634	+11.1 (**0.0091**)	+16.0 (0.1094)	0.6518

*ITT: throughout the study (12 months); PP: follow up phase (6 months)

Paediatric population

Published data related to efficacy and safety studies have not revealed major differences between adults and children suffering from the same disorder.

5.2 Pharmacokinetic properties

Human normal immunoglobulin 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 26 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.

Paediatric population
Published data related to PK studies have not revealed major differences between adults and children suffering from the same disorder.
There are no data on pharmacokinetic properties in paediatric patients with CIDP.

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 injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.
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.
Before use and within the shelf-life, the vials of 50, 100 and 200 ml can be stored at temperature not exceeding 25 °C, for a maximum of 6 consecutive months. The product can no longer be put back in the refrigerator. Discard if not used within the period of 6 months.
The starting date of the storage at temperature not exceeding 25 °C should be reported on the outer box.

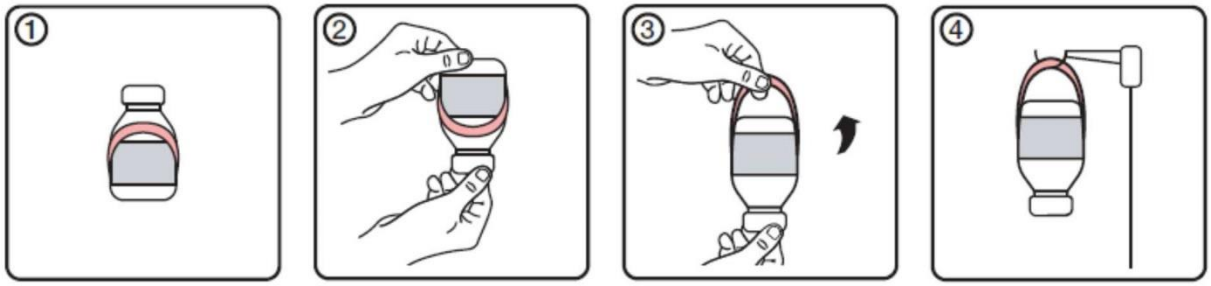
6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use.
The solution should be clear or slightly opalescent, colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.
Solution should be inspected visually for particulate matter and discoloration prior to administration.

Instructions for the use of the hanger



1. Initial status of the vial with hanger label
2. Turn vial upside down
3. Activate the hanger by unfolding it from the label
4. Hang the vial on the infusion stand

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

7 MANUFACTURER

Kedrion S.p.A.
Loc. Ai Conti – Frazione Castelvecchio Pascoli-55051-Barga (LU) Italy.

8 MARKETING AUTHORISATION HOLDER

Kamada Ltd., Beit Kama

9 MARKETING AUTHORISATION NUMBERS

164-11-35926-00

Revised in June 2021 according to MOHs guidelines.