1. NAME OF THE MEDICINAL PRODUCT

KIOVIG 100 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)
One ml contains:

Human normal immunoglobulin ……...100 mg

(purity of at least 98% IgG)

Each vial of 10 ml contains: 1 g of human normal immunoglobulin
Each vial of 25 ml contains: 2.5 g of human normal immunoglobulin
Each vial of 50 ml contains: 5 g of human normal immunoglobulin
Each vial of 100 ml contains: 10 g of human normal immunoglobulin
Each vial of 200 ml contains: 20 g of human normal immunoglobulin
Each vial of 300 ml contains: 30 g of human normal immunoglobulin

Distribution of IgG subclasses (approx. values):

IgG1 ≥ 56.9%
IgG2 ≥ 26.6%
IgG3 ≥ 3.4%
IgG4 ≥ 1.7%

The maximum IgA content is 140 micrograms/ml.

Produced from the plasma of human donors.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear or slightly opalescent and 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 (see section 4.4).
- 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 polyradiculoneuropathy (CIDP).

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.

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and 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 5 to 6 g/L. 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 5-6 g/L is of the order of 0.2-0.8 g/kg/month. The dose 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 infection, it may be necessary to increase the dose 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:
- 0.8-1g/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 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 divided over 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.

The dose 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 maintenance dose: 0.2–0.8 g/kg	every 3–4 weeks to obtain IgG trough level of at least 5–6 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 5-6 g/l
Immunomodulation:		
Primary immune thrombocytopenia	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 5 days
Kawasaki disease	2 g/kg	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	starting dose 2g/kg maintenance dose: 1g/kg	In divided doses over 2-5 days every 3 weeks over 1-2 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.

Method of administration

For intravenous use.

Human normal immunoglobulin should be infused intravenously at an initial rate of 0.5 ml/kg BW/hr for 30 minutes. If well tolerated (see section 4.4), the rate of administration may gradually be increased to a maximum of 6 ml/kg BW/hr. Clinical data obtained from a limited number of patients also indicate that adult PID patients may tolerate an infusion rate of up to 8 ml/kg BW/hr. For further precautions for use see section 4.4.

If dilution prior to infusion is required, KIOVIG may be diluted with 5% glucose solution to a final concentration of 50 mg/ml (5% immunoglobulin). For instructions on dilution of the medicinal product before administration, see section 6.6.

Any infusion-related adverse events should be treated by lowering infusion rates or by stopping the infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

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

Infusion reaction

Certain severe 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. Certain adverse reactions may occur more frequently.

- in case of high rate of infusion
- 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.

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 (0.5 ml/kg BW/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
- monitoring for signs and symptoms of thrombosis
- assessment of blood viscosity in patients at risk for hyperviscosity
- 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.

If dilution of KIOVIG to lower concentrations is required for patients suffering from diabetes mellitus, the use of 5% glucose solution for dilution may have to be reconsidered.

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 infusion of IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypertension, use of estrogens, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, hypercoagulable disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients, patients with diseases which increase blood viscosity, patients with indwelling vascular catheters and patients with high-dose and rapid infusion).

Hyperproteinemia, increased serum viscosity and subsequent relative pseudohyponatremia may occur in patients receiving IVIg therapy. This should be taken into account by physicians, since initiation of treatment for true hyponatremia (i.e. decreasing serum free water) in these patients may lead to a further increase in serum viscosity and a possible predisposition to thromboembolic events.

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. These include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products, age over 65, sepsis, hyperviscosity or paraproteinemia.

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 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 that do not contain these excipients may be considered. KIOVIG does not contain sucrose, maltose or glucose.

Transfusion Related Acute Lung Injury (TRALI)

In patients receiving IVIg there have been reports of acute non-cardiogenic pulmonary edema [Transfusion Related Acute Lung Injury, (TRALI)) in patients administered IVIg (including KIOVIG)]. 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 lifethreatening condition requiring immediate intensive-care-unit management.

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.

From post-marketing data with KIOVIG no clear correlation of AMS to higher doses was observed. Higher incidences of AMS were seen in women.

Haemolytic anaemia

IVIg products can contain blood group antibodies that 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.

Interference with serological testing

After infusion 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).

Administration of KIOVIG can lead to false positive readings in assays that depend on detection of beta-D-glucans for diagnosis of fungal infections. This may persist during the weeks following infusion of the product.

Transmissible agents

KIOVIG is made from human plasma. 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 infectious 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 viruses HAV and 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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Paediatric population

There are no paediatric specific risks with regard to any of the above adverse events. Paediatric patients may be more susceptible to volume overload (see Section 4.9).

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.

Dilution of KIOVIG with a 5% glucose solution may result in increased blood glucose levels.

Loop diuretics

Avoidance of concomitant use of loop diuretics.

Paediatric population

The listed interactions apply both to adults and children.

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 it 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 to be expected.

Breast-feeding

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry. No negative effects on the breastfed newborn/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 KIOVIG. 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 such as chills, headache, dizziness, 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 and rare cases of transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown) have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also Section 4.4).

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

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thromboses.

Cases of Transfusion Related Acute Lung Injury (TRALI).

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 ARs.

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 available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1
Frequency of Adverse Reactions (ADRs) in clinical studies with KIOVIG

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency
Infections and infestations	Bronchitis, nasopharyngitis	Common
	Chronic sinusitis, fungal infection, infection, kidney infection, sinusitis, upper respiratory tract infection, urinary tract infection, bacterial urinary tract infection, meningitis aseptic	Uncommon
Blood and lymphatic system disorders	Anaemia, lymphadenopathy	Common

Table 1 **Frequency of Adverse Reactions (ADRs) in clinical studies with KIOVIG**		
MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
Immune system disorders	Hypersensitivity, anaphylactic reaction	Uncommon
Endocrine disorders	Thyroid disorder	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Common
Psychiatric disorders	Insomnia, anxiety	Common
	Irritability	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness, migraine, paresthesia, hypoesthesia	Common
	Amnesia, dysarthria, dysgeusia, balance disorder, tremor	Uncommon
Eye disorders	Conjunctivitis	Common
	Eye pain, eye swelling	Uncommon
Ear and labyrinth disorders	Vertigo, fluid in middle ear	Uncommon
Cardiac disorders	Tachycardia	Common
Vascular disorders	Hypertension	Very common
	Flushing	Common
	Peripheral coldness, phlebitis	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough, rhinorrhoea, asthma, nasal congestion, oropharyngeal pain, dyspnea	Common
	Oropharyngeal swelling	Uncommon
Gastrointestinal disorders	Nausea	Very common
	Diarrhoea, vomiting, abdominal pain, dyspepsia	Common
	Abdominal distension	Uncommon
Skin and subcutaneous tissue disorders	Rash	Very common
	Contusion, pruritus, urticaria, dermatitis, erythema	Common
	Angioedema, acute urticaria, cold sweat, photosensitivity reaction, night sweats, hyperhidrosis	Uncommon
Musculoskeletal and connective tissue disorders	Back pain, arthralgia, pain in extremity, myalgia, muscle spasms, muscular weakness	Common
	Muscle twitching	Uncommon
Renal and urinary disorders	Proteinuria	Uncommon
General disorders and administration site conditions	Local reactions (e.g. infusion site pain/swelling/reaction/pruritus), pyrexia, fatigue	Very common

Table 1 Frequency of Adverse Reactions (ADRs) in clinical studies with KIOVIG		
MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
	Chills, edema, influenza-like illness, chest discomfort, chest pain, asthenia, malaise, rigors	Common
	Chest tightness, feeling hot, burning sensation, swelling	Uncommon
Investigations	Blood cholesterol increased, blood creatinine increased, blood urea increased, white blood cell count decreased, alanine aminotransferase increased, haematocrit decreased, red blood cell count decreased, respiratory rate increased	Uncommon

Table 2 Post-Marketing Adverse Reactions (ARs)		
MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
Blood and lymphatic system disorders	Haemolysis	Not known
Immune system disorders	Anaphylactic shock	Not known
Nervous system disorders	Transient ischemic attack, cerebral vascular accident	Not known
Cardiac disorders	Myocardial infarction	Not known
Vascular disorders	Hypotension, deep vein thrombosis	Not known
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, pulmonary edema	Not known
Investigations	Coombs direct test positive, oxygen saturation decreased	Not known
Injury, poisoning and procedural complications	Transfusion-related acute lung injury	Not known

Description of selected adverse reactions

Muscle twitching and weakness were reported only in patients with MMN.

Paediatric population

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

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

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

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).

Paediatric population

Smaller children below the age of 5 years may be particularly susceptible to volume overload. Therefore, dosing should be carefully calculated for this population. In addition, children with Kawasaki Disease are at especially high risk due to underlying cardiac compromise so dose and rate of administration should be carefully controlled.

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, but includes immunomodulatory effects.

Paediatric population

There are no theoretical or observed differences in the action of immunoglobulins in children compared to adults.

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 to 5 days equilibrium is reached between the intra- and extravascular compartments.

Pharmacokinetic parameters for KIOVIG were determined in the two clinical studies in PID patients performed in Europe and the US. In these studies, a total of 83 subjects at least 2 years of age were treated with doses of 300 to 600 mg/kg body weight every 21 to 28 days for 6 to 12 months. The median IgG half-life after administration of KIOVIG was 32.5 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency. Pharmacokinetic parameters for the product are summarized in the table below. All parameters were analysed separately for three age groups, children (below 12 years, n=5), adolescents (13 to 17 years, n=10), and adults (above 18 years of age, n=64). The values obtained in the studies are comparable to parameters reported for other human immunoglobulins.

Summary of KIOVIG pharmacokinetic parameters						
Parameter	**Children (12 years or below)**		**Adolescents (13 to 17 years)**		**Adults (18 years or above)**	
	Median	**95% CI***	**Median**	**95% CI**	**Median**	**95% CI**
Terminal half-life (days)	41.3	20.2 to 86.8	45.1	27.3 to 89.3	31.9	29.6 to 36.1
C_{min} (mg/dl)/(mg/kg) (trough level)	2.28	1.72 to 2.74	2.25	1.98 to 2.64	2.24	1.92 to 2.43

C_{max} (mg/dl)/(mg/kg) (peak level)	4.44	3.30 to 4.90	4.43	3.78 to 5.16	4.50	3.99 to 4.78
In-vivo recovery (%)	121	87 to 137	99	75 to 121	104	96 to 114
Incremental recovery (mg/dl)/(mg/kg)	2.26	1.70 to 2.60	2.09	1.78 to 2.65	2.17	1.99 to 2.44
$AUC_{0\text{-}21d}$ (g·h/dl) (area under the curve)	1.49	1.34 to 1.81	1.67	1.45 to 2.19	1.62	1.50 to 1.78

*CI – Confidence Interval

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.

The safety of KIOVIG has been demonstrated in several non-clinical studies. Non-clinical data reveal no special risk for humans based on conventional studies of safety pharmacology and toxicity.

Studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction in animals are impracticable due to induction of and interference by developing antibodies to heterologous proteins. Since clinical experience provides no evidence for carcinogenic potential of immunoglobulins, no experimental studies in heterogeneous species were performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
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.

If dilution to lower concentrations is required, immediate use after dilution is recommended. The in-use stability of KIOVIG after dilution with a 5% glucose solution to a final concentration of 50 mg/ml (5%) immunoglobulin has been demonstrated for 21 days at 2°C to 8°C as well as 28°C to 30°C; however, these studies did not include the microbial contamination and safety aspect.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10, 25, 50, 100, 200 or 300 ml of solution in a vial (Type I glass) with a stopper (bromobutyl).
Pack size: 1 vial

Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

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

If dilution is required, 5% glucose solution is recommended. For obtaining an immunoglobulin solution of 50 mg/ml (5%), KIOVIG 100 mg/ml (10%) should be diluted with an equal volume of the glucose solution. It is recommended that during dilution the risk of microbial contamination is minimised.

The product should be inspected visually for particulate matter and discolouration prior to administration. The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.

KIOVIG should only be administered intravenously. Other routes of administration have not been evaluated.

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

7. REGISTRATION HOLDER AND IMPORTER

Takeda Israel Ltd.,
25 Efal st., Petach Tikva 4951125

8. REGISTRATION NUMBER

146-45-33157-00

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