Baxalta

Kiovig

NAME OF THE MEDICINAL PRODUCT
KIOVIG 100 mg/ml solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml contains:
Human normal immunoglobulin (IVIg).....100 mg*
*corresponding to human protein content, of which at least 98% is IgG
One vial of 10 ml contains: 1 g
One vial of 25 ml contains: 2.5 g
One vial of 50 ml contains: 5 g
One vial of 100 ml contains: 10 g
One vial of 200 ml contains: 20 g
One vial of 300ml contains: 30g

Distribution of IgG subclasses:
IgG1 ≥ 56.9%
IgG2 ≥ 26.6%
IgG3 ≥ 3.4%
IgG4 ≥ 1.7%
Maximum immunoglobulin A (IgA) content: 0.14 milligram per ml.

Excipient: Glycine
For a full list of excipients, see ‘List of excipients’.

PHARMACEUTICAL FORM
Solution for infusion
The solution is clear or slightly opalescent and colourless or pale yellow.

CLINICAL PARTICULARS
Therapeutic indications
Replacement therapy in
Primary immunodeficiency syndromes such as:
- congenital agammaglobulinaemia and hypogamma-globulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia (CLL) with severe secondary hypogamma-globulinaemia and recurrent infections.
Children with congenital AIDS and recurrent infections.

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

Allogeneic bone marrow transplantation

Posology and method of administration
Replacement therapy should be initiated and monitored under a physician experienced in the treatment of immunodeficiency.

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

Replacement therapy in primary immunodeficiency syndromes
The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4-6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4-0.8 g/kg body weight (BW) followed by at least 0.2 g/kg BW every three weeks.
The dose required to achieve a trough level of 6 g/l is of the order of 0.2-0.8 g/kg BW/ month. The dosage interval when steady state has been reached varies from 2 to 4 weeks.
Trough levels should be measured in order to adjust the dose and dosage interval.

Replacement therapy in myeloma or chronic lymphocytic leukaemia (CLL) with severe secondary hypogamma-globulinaemia and recurrent infections; replacement therapy in children with congenital AIDS and recurrent infections
The recommended dose is 0.2-0.4 g/kg BW every three to four weeks.

Idiopathic Thrombocytopenic Purpura (ITP)
For the treatment of an acute episode, 0.8-1 g/kg BW on day one, which may be repeated once within 3 days, or 0.4 g/kg BW daily for two to five days. The treatment can be repeated if a relapse occurs.

Guillain Barré Syndrome
0.4 g/kg BW/day for 3 to 7 days.
Experience in children is limited.

Kawasaki Disease

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

Multifocal Motor Neuropathy (MMN)

Starting dose: 2 g/kg given over 2 – 5 days.
Maintenance dose: 0.5 – 2.4 g/kg every month based on clinical response.

Allogeneic Bone Marrow Transplantation

Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant.
For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The starting dose is normally 0.5 g/kg BW/week, starting seven days before transplantation and for up to 3 months after transplantation.
In case of persistent lack of antibody production, dosage of 0.5 g/kg BW/month is recommended until the antibody level returns to normal.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injections
Replacement therapy in primary immunodeficiency	starting dose: 0.4 – 0.8 g/kg BW thereafter: 0.2 – 0.8 g/kg BW	every 2 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 – 0.4 g/kg BW	every 3 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/l
Children with AIDS	0.2 – 0.4 g/kg BW	every 3 – 4 weeks
Immunomodulation: Idiopathic thrombocytopenic purpura	0.8 – 1 g/kg/BW or 0.4 g/kg/BW/d	on day 1, possibly repeated once within 3 days for 2 – 5 days
Guillain Barré syndrome	0.4 g/kg/BW/d	for 3 – 7 days
Kawasaki disease	1.6 – 2 g/kg/BW or 2g/kg/BW	in several doses for 2 – 5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid

Multifocal Motor Neuropathy (MMN)	starting dose: 2 g/kg maintenance dose: 0.5 – 2.4 g/kg	given over 2 – 5 days every month depending on clinical response
Allogenic bone marrow transplantation - Treatment of infections and prophylaxis of graft versus host disease - Persistent lack of antibody production	0.5 g/kg BW 0.5 g/kg BW	every week from day -7 up to 3 months after transplantation every month until antibody levels return to normal

Method of administration

Human normal immunoglobulin should be infused intravenously at an initial rate of 0.5 ml/kg BW/hr for 30 minutes. If well tolerated, 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 'Special warnings and precaution for use'.

In patients at risk for acute renal failure or thromboembolic adverse reactions, KIOVIG should not be infused rapidly.

In general, it is recommended that patients beginning treatment with KIOVIG or switching from one intravenous immunoglobulin (IVIg) brand to KIOVIG be started at the lowest rate and then increased to the maximal rate if they have tolerated several infusions at intermediate rates of infusion.

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

Certain adverse reactions such as headaches and flushing may be related to the rate of infusion. Slowing or stopping the infusion usually allows the symptoms to disappear promptly. The infusion may then be resumed at a rate that does not result in recurrence of the symptoms. (See 'Adverse Reactions')

Adverse reactions may occur more frequently in immune deficient patients, who receive human normal immunoglobulin for the first time, when they switch from another IVIg brand, or when there has been a long interval since the previous infusion. (See 'Adverse Reactions')

KIOVIG is recommended for infusion at a concentration of 10%. If KIOVIG must be diluted, 5% glucose solution should be used as a diluent. For details on dilution, see 'Special precautions for disposal and other handling'.

Contraindications
KIOVIG is contraindicated in patients with known anaphylactic or severe hypersensitivity responses to Immunoglobulin (Human) or to any of its excipients.

KIOVIG is contraindicated in patients who are deficient in IgA and have developed anti-IgA antibodies. Patients with severe IgA deficiency (IgA < 0.05 g/l) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis has been reported with the use of KIOVIG even though it contains low amounts of IgA (average concentration of 37 mcg/ml).

Special warnings and precautions for use
Certain severe adverse reactions may be related to the rate of infusion (see section 'Adverse Reactions'). The recommended infusion rate given under "Method of administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently
- in case of high rate of infusion
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency
- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin by first infusing 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 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 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.
In case of shock, standard medical treatment for shock should be implemented.

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.

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

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies. IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

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

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 thrombosis 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, 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).

The potential risks and benefits of immunoglobulins should be weighed against those of alternative therapies for all patients for whom immunoglobulins administration is being considered. Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity assessed.

Hyperproteinaemia, Hyponatremia and Increased Serum Vicosity

Hyperproteinaemia, increased serum viscosity and hyponatraemia may occur in patients receiving IVIg therapy, including KIOVIG. It is clinically critical to distinguish true hyponatraemia from a pseudohyponatremia that is associated with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum-free water in

patients with pseudohypoatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.

Renal Adverse Reactions

Severe renal adverse reactions 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 preexisting renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products, age over 65, sepsis or paraproteinaemia.

In case of renal impairment, IVIg discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose, 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.

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

Transfusion Related Acute Lung Injury (TRALI)

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

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

Aseptic meningitis syndrome (AMS)

An aseptic meningitis syndrome (AMS) has been reported to occur in association with IVIg (including KIOVIG) 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 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.

Haemolytic anaemia

KIOVIG contains blood group antibodies that may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin. This may cause a positive direct antiglobulin test [DAT (Coombs' test)]. Delayed haemolytic anaemia can develop subsequent to IVIg (including

KIOVIG) therapy due to enhanced red blood cells sequestration; acute haemolysis, consistent with intravascular haemolysis, has been reported. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. See ‘Adverse Reactions'.

The following risk factors may be related to the development of haemolysis: high doses (single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of haemolysis but its role is uncertain.

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, for example, Hepatitis A, Hepatitis B, measles, and varicella.

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
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.

It is strongly recommended that every time that KIOVIG 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.

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.

Pregnancy, Lactation and Fertility

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 lactating 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.

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Physicians should balance the potential risks and only prescribe KIOVIG if clearly needed.

The effects of KIOVIG on fertility have not been established in controlled clinical trials.

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.

Adverse Reactions

Summary of the safety profile

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

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

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

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

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

Two clinical trials with KIOVIG were performed in primary immunodeficiency (PID) patients in Europe and the US. In the European study, 22 subjects with hypo- and agammaglobulinaemia received KIOVIG for about 6 months. The US clinical trial was performed with 61 subjects with PID, who received KIOVIG for about 12 months. In Europe, an additional clinical studyin 23

patients with idiopathic thrombocytopenic purpura (ITP) was performed. No serious adverse reaction (AR) was observed during the studies, with the exception of two episodes of aseptic meningitis in one patient of the US PID study, which were deemed possibly related to the medicinal product. Most ARs observed were mild to moderate in nature.

In the European and US PID studies the overall rate of ARs per infusion was 0.27. As expected due to the much higher dosage, the AR rate per infusion was higher (0.49) in the ITP trial; 87.5% of these ARs were assessed as mild. The ARs reported in the three studies and post-marketing are summarized and categorized according to the MedDRA System organ class and frequency in the table below.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated using 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, undesirable effects are presented in order of decreasing seriousness.

Frequency of adverse reactions (ARs)		
MedDRA system organ class	**MedDRA preferred term**	**AR frequency category**
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	Uncommon
	Meningitis aseptic	Rare
Blood and lymphatic system disorders	Anaemia, lymphadenopathy	Uncommon
	Haemolysis	Not known
Immune system disorders	Anaphylactic shock, anaphylactic reaction, hypersensitivity	Not known
Endocrine	Thyroid disorder	Uncommon

disorders		
Psychiatric disorders	Anxiety	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness, migraine	Common
	Amnesia, burning sensation, dysarthria, dysgeusia, insomnia	Uncommon
	Transient ischemic attack, tremor	Not known
	Conjunctivitis, eye pain, eye swelling	Uncommon
Ear and labyrinth disorders	Vertigo	Common
	Fluid in middle ear	Uncommon
Cardiac disorders	Tachycardia	Common
Vascular disorders	Flushing, hypertension	Common
	Peripheral coldness, phlebitis	Uncommon
	Deep vein thrombosis, hypotension	Not known
Respiratory, thoracic and mediastinal disorders	Cough, rhinorrhoea	Common
	Asthma, nasal congestion, oropharyngeal swelling, pharyngolaryngeal pain	Uncommon
	Pulmonary embolism, pulomonary oedema, dyspnoea	Not known
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Common
	Abdominal pain	Not known
Skin and subcutaneous tissue disorders	Pruritus, rash, urticarial	Common
	Angioneurotic oedema, acute urticaria, cold sweat, contusion, dermatitis, erythematous rash, pruritic rash	Uncommon
	Hyperhidrosis	Not known
Musculoskeletal and connective tissue disorders	Back pain, myalgia, pain in extremity	Common
	Muscle spasms	Uncommon
General disorders and	Pyrexia	Very common

administration site conditions	Fatigue, influenza-like illness, infusion site pain, infusion site swelling, rigors,	Common
	Application site pruritus, chest tightness, feeling hot, infusion site phlebitis, infusion site reaction, infusion site tenderness, malaise, peripheral oedema, swelling	Uncommon
	Chest pain, chills	Not known
Investigations	Body temperature increased	Common
	Blood cholesterol increased, blood creatinine increased, blood urea increased, haematocrit decreased, red blood cell count decreased, respiratory rate increased, white blood cell count decreased	Uncommon
	Coombs direct test positive, oxygen saturation decreased	Not known
Injury, poisoning and procedural complications	Transfusion-related acute lung injury	Not known

For safety with respect to transmissible agents, see 'Special warnings and precautions for use'.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02

Human normal immunoglobulin contains mainly functionally intact 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 IgG subclasses closely proportional to that in native human plasma. Adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range.
The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

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 summarised 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
$_{AUC0\text{-}21d}$ (g.h/dl) (area under 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.

Preclinical safety data
Immunoglobulins are normal constituents of the human body.
The safety of KIOVIG has been demonstrated in several non-clinical studies. Nonclinical 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.

PHARMACEUTICAL PARTICULARS

List of excipients
Glycine
Water for injections

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in ‘Special precautions for disposal and other handling’.

Shelf life
2 years.

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.

Special precautions for storage
Store in a refrigerator (2°C – 8°C).
Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

During the shelf life, the product may be stored at room temperature (not more than 25°C) for up to 12 months. The date of transfer to room temperature and the end of the 12-month period should be recorded on the outer carton. Once the product is stored at room temperature it must not be returned to the refrigerator and must be discarded, if not used by the end of the 12-month period.

Nature and contents of container
10, 25, 50, 100, 200 or 300 of solution in a vial (Type I glass) with a stopper.
Pack size: 1 vial
Not all pack sizes may be marketed.

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. Do not use if particulate matter or discolouration is observed.
Only clear to slightly opalescent and colourless to pale yellow solutions are to be administered.

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

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

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DATE OF REVISION OF THE TEXT
JANUARY 2017