

PRODUCT INFORMATION

Kiovig 10% will be funded and supplied under the national blood arrangements only as an IVIg product at this time.

PRODUCT INFORMATION KIOVIG

NAME OF THE MEDICINE

Kiovig

Chemical Name

Normal Immunoglobulin (human)

Composition

Table 1: Composition of the KIOVIG 10% (w/v) [Immunoglobulin G (IgG) 100 mg/mL]

Name of the components	Nominal values per vial expressed as protein with at least 98% IgG contents.				
	10mL (g/10mL)	25mL (g/25mL)	50mL (g/50mL)	100mL (g/100mL)	200mL (g/200mL)
Active Ingredient:					
Normal Immunoglobulin (human), contains at least 98% IgG	1.0	2.5	5.0	10.0	20.0
Stabilising agent:					
Glycine	187.5mg 4.6 to 5.1	468.75mg 4.6 to 5.1	937.5mg 4.6 to 5.1	1.88g 4.6 to 5.1	3.75g 4.6 to 5.1
Water for Inject. qs	10mL	25mL	50mL	100mL	200mL

* pH is measured after the solution is diluted to 1% protein with saline. The pH range of 4.6 to 5.1 corresponds to a range of 4.4 to 4.9 when the solution is measured undiluted.

DESCRIPTION

The active ingredient in KIOVIG is a human plasma-derived Immunoglobulin, concentration of 100mg/mL (10% w/v), produced from large pools of human plasma by a modified Cohn-Oncley cold ethanol fractionation, yielding an intermediate immunoglobulin G, referred to as Precipitate G. During the cold ethanol plasma fractionation manufacturing process, the level of viral burden in a plasma pool has been largely reduced to a certain extent, as demonstrated by viral spiking experiment. Precipitate G is further purified by means of a weak cation-exchange and anion-exchange chromatography.

To reduce further a possible viral transmission to a minimal level, a triple step of viral inactivation (TVR inactivation), [solvent detergent (S/D), nano-filtration (35nm), and incubation at a low pH and elevated temperature (30°C to 32°C, pasteurisation for 21 to 23 days) was incorporated into the downstream purification. Thus, the active ingredient formulated in KIOVIG has been subjected to a rigorous elimination for both lipid and non-lipid enveloped viruses.

The manufacturing processes do not affect the composition of the immunoglobulin in the normal human plasma origin. The distribution of the IgG sub-classes formulated in this product comprises IgG ≥ 56.9%, IgG₂ ≥ 26.6%, IgG₃ ≥ 3.4%, IgG₄ ≥ 1.7%. It contains immunoglobulin A (IgA) at a trace level, which is not more than 0.14 mg/mL. The preparation is a sterile, nonpyrogenic, isotonic solution with Osmolality of 240 to 300 mOsmol/kg and a pH of 4.6 to 5.1. At this low pH the formation of the IgG aggregates is much reduced, leading to in reducing the incidence of infusion-related adverse reactions. It contains glycine acting as a stabilising agent of the proteins. The product does not contain preservative.

Chemical Structures

The active ingredient in KIOVIG is a human polyvalent IgG. Immunoglobulins are made up of four polypeptide chains, comprising two identical light chains of a molecular weight of approximately 25kD and two identical heavy chain of molecular weight of approximately 50kD. The four chains form a three-dimensional Y-shaped structure as shown by X-ray crystallography. Carbohydrate groups are attached covalently at a distinct position of the heavy chains. The overall molecular weight of IgG is approximately 150kD.

Immunoglobulin G antibodies are the most common immunoglobulin class, with a level of 9–12 gram per litre of plasma, accounting for about 75% of the total immunoglobulins in plasma of healthy individuals. Immunoglobulin G is further divided into subclasses with different heavy chain isotypes: IgG₁, IgG₂, IgG₃, and IgG₄.

PHARMACOLOGY

Immunological Mode of Action

IgG antibodies are protein molecules that are capable of specific interaction with molecules that are part of the membranes of infectious agents, foreign or abnormal cells, or toxic materials (antigens). Antibodies are produced by B lymphocytes, often with the help of T lymphocytes, macrophages, or dendritic cells. Following an initial interaction, some of the B-cells differentiate to memory cells, which upon encountering with the same infectious agent later in life, are capable of rapidly reproducing and producing increased quantities of the IgG antibodies specific to the same infectious agent.

The IgG molecules have two distinct and separable functions. One function is to bind specifically to the epitope in the antigen through the Fab end of the molecule, which is formed by the combination of the heavy and light chains. The other end of the IgG molecule, the Fc portion, can activate complement, bind to receptors on phagocytic cells to promote engulfment of the antigen/antibody complexes, and binding to the neonatal receptor which modulates the catabolism of IgG. In addition, binding of the Fc portion of the IgG molecule to regulatory receptors on B cells, T cells, and macrophages can modulate the activity of those cells, which may be useful in the control of autoimmune disease.

Thus, the mode of action of immunoglobulin IV (IGIV) mimics the action of the normal plasma immunoglobulin in a healthy adult individual having a broad spectrum of antibodies against infectious agents. As the active ingredients in KIOVIG, IgG 10% w/v is a plasma-derived immunoglobulin isolated from a pool plasma of healthy donors, this product can be classified as a replacement therapy in patients who are unable to produce sufficient amount of IgG antibodies. Adequate doses of this medicinal product may restore the abnormally low immunoglobulin G levels of immune deficient patients to a normal range.

CLINICAL TRIALS

Pharmacokinetic Properties

- **Intravenous Administration:** Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is rapidly and nearly evenly

distributed between plasma and extravascular fluid; after approximately 3–5 days equilibrium is reached between the intra- and extravascular compartments.

Pharmacokinetic parameters for KIOVIG were assessed, in a prospective, open-label, non-controlled, multi-center study design, **Clinical Study 160001**, in 22 subjects suffering from primary immunodeficiency (PID) with a clinical condition as hypo- and agammaglobulinemia. Subjects were initially treated with three infusions of GAMMAGARD S/D at a dose of 300 to 450 mg/kg body weight/ infusion given every 3 weeks to standardise the IgG replacement therapy of all subjects to the same intravenous product and to acquire data with a licensed product. This is followed by treatment with KIOVIG of 10% IgG Solution with a dose of 300–450 mg/kg body weight/3 weeks for the remaining 9 infusions.

These regimens have been shown are adequate to maintain IgG trough levels at or above the typically accepted threshold of 400 to 600 mg/dL. All pharmacokinetic parameters were calculated for individual subjects for total IgG and IgG subclasses (IgG₁, IgG₂, IgG₃ and IgG₄), whilst for the vivo recovery was assessed only on the basis of the total IgG plasma level.

The results of the pharmacokinetic parameters are shown in Table 2. As shown in the table, KIOVIG had a half-life of about 30 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency. The values obtained are comparable to parameters reported for other human immunoglobulins.

Table 2: Summary of KIOVIG Pharmacokinetic Parameters

Parameters	Number of Patients (N)	Median	95% Confidence Interval
Terminal half-life (days)	22	30.1	27.1 : 43.3
Cmin (mg/dL) (trough level)	22	848	772 : 1000
Cmax (mg/dL) (peak level)	22	1630	1470 : 1750
In-vivo recovery (%)	22	89	84 : 101
Incremental recovery (mg/dL/(mg/kg))	22	1.85	1.71 : 2.14
Tmax (hours) (time to reach peak)	22	0.25	0.25 : 0.25
AUC _{0-21d} (g.h/dL) (area under the curve)	22	545	490 : 603

• **Subcutaneous Administration:** Pharmacokinetic (PK) parameters of subcutaneously administered KIOVIG were evaluated in subjects with primary immunodeficiency (PI) who were 12 years and older during a clinical study (see *Clinical Study of Subcutaneous Administration*). Subjects were treated intravenously for 12 weeks with KIOVIG and then switched to weekly subcutaneous KIOVIG infusions. Initially, all subjects were treated for a minimum of 12 weeks at a subcutaneous dose that was 130% of the intravenous dose. A comparison of the area under the curve (AUC) for intravenous and subcutaneous infusions done on the first 15 adult subjects determined that the subcutaneous dose required to provide an exposure from subcutaneous administration that was not inferior to the exposure from intravenous administration was 137% of the intravenous dose. Subsequently, all subjects were treated with this dose for 6 weeks after which the dose was individualised for all subjects using the trough IgG levels, as described below. After a minimum of 8 weeks at this subcutaneous dose, the PK evaluation was conducted on 32 subjects 12 years of age or older. The mean adjusted dose at the end of the study was 137.3% (125.7–150.8) of the intravenous dose for subjects 12 years and older, and 141.0% (100.5 to 160.0) for subjects under the age of 12. Thus, there was not a significant dosing difference required for children. At this dose adjustment, the geometric mean ratio of the AUC for subcutaneous vs. intravenous KIOVIG administration was 95.2% (90% confidence limit 92.3 to 98.2). The peak IgG level occurred 2.9 (1.2 to 3.2) days after subcutaneous administration.

The pharmacokinetic parameters of KIOVIG administered intravenously compared to subcutaneously in the clinical trial are shown in Table 3. The mean peak IgG levels were lower (1393 ± 289 mg/dL) during subcutaneous treatment with KIOVIG compared to when it was administered intravenously (2240 ± 536 mg/dL), consistent with the lower weekly dose compared to the dose administered every 3 or 4 weeks intravenously. In contrast, the mean trough levels were higher with KIOVIG given subcutaneously (1202 ± 282 mg/dL), compared to those when given intravenously (1050 ± 260 mg/dL), a result of both higher monthly dose and more frequent dosing.

Table 3: Pharmacokinetic Parameters of Subcutaneously Administered KIOVIG Compared to KIOVIG Administered Intravenously

	Subcutaneous Administration	Intravenous Administration
Number of Subjects	32	32
Dose ¹ (mg/kg) Mean ± SD Range (min to max)	182.6 ± 48.4 94.2 to 293.8	133.2 ± 36.9 62.7 to 195.4
IgG Peak Levels (mg/dL) Mean ± SD Range (min to max)	1393 ± 289 734 to 1900	2240 ± 536 1130 to 3610
IgG Trough Levels (mg/dL) Mean ± SD Range (min to max)	1202 ± 282 621 to 1700	1050 ± 260 532 to 1460
AUC ² (days*mg/dL) Mean ± SD Range (min to max)	9176 ± 1928 4695 to 12468	9958 ± 2274 5097 to 13831
Clearance [mL/kg/day] Mean ± SD Range (min to max)	2.023 ± 0.528 1.225 to 3.747	1.355 ± 0.316 0.880 to 2.340

1. Weekly equivalent dose; 2. Standardised to a 7 day interval

Clinical Efficacy

• **Clinical Studies of Intravenous (IV) Administration:** Efficacy and safety of KIOVIG, 10% IGIV solution, was assessed in three clinical studies, a European study in 22 patients with hypo- or agammaglobulinemia, a US study in 61 patients with primary immunodeficiencies (IPD), and a European study in 23 patients with idiopathic thrombocytopenia purpura (ITP). None of these studies were designed to compare KIOVIG with another IGIV product. The use of KIOVIG, 10% IGIV solution in patients with Primary Immunodeficiency is supported by Phase 3 clinical **Study 160101** in subjects who were treated with 300 to 600 mg/kg every 21 to 28 days for 12 months. The 61 subjects in this study were between 6 to 72 years of age, 54% female and 46% male, and 93% Caucasian, 5% African-American, and 2% Asian. The description of this study is shown in Table 4.

Table 4: Summary of patient demographics for the US Clinical trials in PID (160101)

Study Number	Trial design	Dosage, route of administration and duration	Study subjects	Median age (range)	Gender
160101	Randomises, double-blinded, uncontrolled, multicenter	300–600mg/kg b.w. every 21–28 days; I.V. one year, with the option to continue treatment.	61 subjects with PID, older than 24 months of age were treated.	Median age: 34 years, Range: 6–72 years	Females: N=33 Males: N=28

Three subjects were excluded from the protocol analysis due to non-study product related reasons. The primary efficacy endpoint was the annualised rate of specified acute serious bacterial infections, i.e. the mean number of specified acute serious bacterial infections per subject per year (Table 5).

Table 5: Summary of Validated Acute Serious Bacterial Infections for the Per-Protocol Analysis

	Number of Events
Validated Infections ^a	
Bacteremia/Sepsis	0
Bacterial Meningitis	0
Osteomyelitis/Septic Arthritis	0
Bacterial Pneumonia	0
Visceral Abscess	0
Total	0
Hospitalisation Secondary to Infection	0
Mean Number of Validated Infections per Subject/year	0
p-value ^b 95% Confidence Interval ^b	p < 0.0001 (0.000, 0.064)

^a Serious acute bacterial infections were defined by FDA and met specific diagnostic requirements.

^b The rate of validated infections was compared with a rate of 1 per subject per year, in accordance with recommendations by the FDA Blood Products Advisory Committee.

The secondary efficacy endpoints in this study were the annualised rate of other specified validated bacterial infections and the number of hospitalisations secondary to infectious complications (see Table 6). In this study, there were no validated acute serious bacterial infections in any of the treated subjects. The annualised rate of acute serious bacterial infections was significantly less than (p < 0.0001) the rate of

one infection per year, in accordance with recommendations by the FDA Blood Products Advisory Committee. Four of the 61 subjects reported a total of 4 other specified validated bacterial infections. None were serious or severe, none resulted in hospitalisation, and all resolved completely.

Table 6: Summary of validated other Bacterial Infections

	Number of Events
Validated Infections ^a	
Urinary tract infection	1
Gastroenteritis	1
Lower Respiratory Tract Infection: tracheobronchitis, bronchitis without evidence of pneumonia	0
Lower Respiratory Tract Infection: Other infections (e.g., lung abscess, Empyema)	0
Otitis media	2
Total	4
Hospitalisations secondary to Infection	0
Mean Number of validated Infections per Subject per year, with 95% Confidence Interval	0.07 (0.018, 0.168)

^a Other bacterial infections that met specific diagnostic requirements.

The rate of all clinically-defined but non-validated infections was 3.4 infections per patient per year. These consisted primarily of recurrent episodes of commonly infections in this patient population (sinusitis, bronchitis, nasopharyngitis, urinary tract infections, and upper respiratory infections).

• **Clinical Study of Subcutaneous (SC) Administration:** A prospective, open-label, non-randomised, multi-center study was conducted to determine the pharmacokinetic equivalence of KIOVIG subcutaneous infusion in 49 adult and paediatric subjects with PID. Rates of acute serious bacterial infections, overall infection rate, safety and tolerability were analysed as secondary efficacy endpoints. All subjects were treated for 12 weeks with KIOVIG intravenous infusion every 3 or 4 weeks. Subjects who were on intravenous therapy prior to entering the study were switched to KIOVIG at the same dose and frequency. Subjects who were receiving subcutaneous immunoglobulin were switched to KIOVIG at the intravenous dose they had been given prior to switching to subcutaneous therapy. A PK analysis was performed at the end of the intravenous period in all subjects aged 12 years and older.

One week after the last intravenous infusion, each subject began subcutaneous therapy with KIOVIG at 130% of the weekly equivalent of the intravenous dose for a minimum of 12 weeks. PK data from the first 15 adult subjects were used to determine the dose required to ensure that the IgG exposure with subcutaneous therapy was not inferior to that with intravenous therapy. The median dose determined from these subjects was 137% of the intravenous dose, and subsequently all subjects were treated for a minimum of 6 weeks at this dose. After 6 subcutaneous infusions, a trough IgG level was obtained and used to individually adapt the subcutaneous dose of KIOVIG to compensate for individual variation from the mean value of 137%. All subjects received a minimum of 12 infusions at this individually adapted dose. Following the formal protocol, all subjects continued to receive subcutaneous treatment with KIOVIG until the last subject completed the study. There were 47 subjects treated with 2,294 subcutaneous infusions of KIOVIG: 4 subjects treated for up to 29 weeks, 17 subjects for 30 to 52 weeks, and 26 subjects for 53 weeks or longer. The median duration of subcutaneous treatment was 379 days (range: 57 to 477 days).

Efficacy was determined throughout the entire subcutaneous phase. There were 31 adults 16 years or older, 4 adolescents between 12 and <16 years of age, and 14 children between 2 years and <12. The volume of KIOVIG infused was 30 mL per site for patients weighing 40 kg or more, and 20 mL per site for those weighing less than 40 kg. The total weekly dose was divided by those values to determine the number of sites.

Mean weekly subcutaneous doses ranged from 181.9 mg/kg to 190.7 mg/kg (at 130% to 137% of the intravenous dose). In the study, the number of infusion sites per infusion was dependent on the dose of IgG and in 73% of infusions, the number of infusion sites was 5 or fewer.

There were 3 serious validated bacterial infections, all bacterial pneumonia. None of these subjects required hospitalisation to treat their infection. The annual rate of acute serious bacterial infections while on KIOVIG subcutaneous treatment was 0.067, with an upper 99% confidence limit of 0.133, which is lower than the minimal goal of

achieving a rate of <1 bacterial infection per patient-year.

The summary of infections and associated events for subjects during subcutaneous therapy with KIOVIG is summarised in Table 7. The annual rate of any infection in this study during subcutaneous therapy, including viral and fungal infections, was 4.1 infections per subject per year. This is consistent with the rate of infections observed in other clinical studies of intravenous and subcutaneous immunoglobulin.

Table 7: Summary of Infections and Associated Events

Number of subjects (efficacy phase)	47
Total number of subject years	44
Annual rate of any infections	4.1 (95% CI 3.2 to 5.1) infections/subject year
Antibiotic use [§] (prophylaxis or treatment)	
Number of subjects (%)	40 (85.1%)
Annual rate	50.2 (95% CI 33.4 to 71.9) days/subject year
Days out of work/school/ day care or unable to perform normal activities	
Number of subjects (%)	25 (53.2%)
Annual rate	4.0 (95% CI 2.5 to 6.1) days/subject year
Hospitalisations due to infections	
Number of subjects (%)	0 (0.0%)
Annual rate	0.0 (95% CI 0.0 to 0.1) days/subject year

[§] Included systemic and topical antibacterial, anti-fungal, anti-viral, and anti-protozoal antimicrobials.

INDICATIONS

KIOVIG administered Intravenously is indicated for:

- Replacement therapy indications
 - Primary immunodeficiency disorders (PID);
 - Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.
- Immunomodulation indications
 - Idiopathic thrombocytopenia purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count;
 - Guillain Barré syndrome;
 - Kawasaki Disease.

KIOVIG administered Subcutaneously is indicated for:

- Replacement therapy indications
 - Primary immunodeficiency disorders (PID).

CONTRA-INDICATIONS

KIOVIG, IgG 10% Solution is contraindicated in patients with known anaphylactic or severe hypersensitivity responses to Immunoglobulin (human). Patients with severe selective IgA deficiency (IgA < 0.05g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction.

Anaphylaxis can occur using KIOVIG, IgG 10% Solution even though it contains low amounts of IgA (average concentration of 37µg/mL). These patients should be treated only if their IgA deficiency is associated with an immune deficiency for which therapy with intravenous immunoglobulin (IGIV) is clearly indicated. Such patients should only receive intravenous immunoglobulin with utmost caution and in a setting where supportive care is available for treating life-threatening reactions.

PRECAUTIONS

Infusions of gammaglobulin have been associated with thromboembolic events and impaired renal function, including acute renal failure. Risk is increased in patients with pre-existing impaired renal function and cardiovascular risk factors such as hypertension, history of cardiac disease, hyperviscosity, poor ambulation. Risk of these events may be increased with rapid rates of infusion and high (1–2g/kg) doses of IgG. Risk can be reduced by ensuring adequate hydration and using slower rates of infusion in patients considered to be at high risk of renal dysfunction or cardiovascular disease. In subjects with impaired renal function consider monitoring urine output and serum creatinine, and avoiding loop diuretics and sucrose containing IGIV products.

Intravenous infusions of IGIV have been associated with an aseptic meningitis syndrome with severe headache, nuchal rigidity, CSF pleocytosis and elevated CSF protein. Symptoms can begin during and up to 48 hours after an infusion. It is thought that the risk is increased with higher (1–2g/kg) doses of IGIV and in subjects with frequent headaches, especially migraine headaches. Consider slower rates of infusion for such patients.

In case of these events, 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.

It is recommended that SC infusions not be given to patients with ITP due to the increased risk of bleeding and hematoma.

Infusion-related precautions

Certain adverse reactions such as headache, flushing and changes in pulse rate and blood pressure may be related to the rate of infusion (see *Dosage and Administration*). The recommended infusion rate given under "Dosage and Administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

In particular, slower rates of infusion should be considered for the following:

- patients with hypo- or agammaglobulinemia with or without IgA deficiency;
- patients who receive human normal immunoglobulin for the first time or, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion;
- patients at risk for acute renal failure or thromboembolic adverse reactions;
- patients who have underlying renal disease or who are judged to be at risk of developing thrombotic events.

Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV products, including KIOVIG. It is clinically critical to distinguish true hyponatremia 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 pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a possible predisposition to thromboembolic events.

Viral transmission

This product is manufactured using components of human blood, which may contain the causative agents of hepatitis and other viral diseases, and theoretically Creutzfeldt-Jacob Disease (CJD) agents. Prescribed manufacturing procedures utilised at the plasma collection centers and plasma-testing laboratories are designed to reduce the risk of transmitting viral infection.

Important elements of the rigorous screening include: careful selection of donors for plasma pools, viral testing at multiple stages, and the application of a rigorously validated method of testing. Prior to the manufacturing of the bulk drug substance, the plasma pool is tested for viral markers using HIQ-PCR method (Hyland Immuno Quality Assured Polymerase Chain Reaction is nucleic acid amplification test, NAT), which allows for the detection of viruses at a level of 500 genome equivalents (ge) per mL of the plasma.

The inclusion of Solvent Detergent (S/D) into the manufacturing process, which is effective for removal of enveloped-lipid viruses (HIV-1, HBV and HCV) and nanofiltration and incubation at elevated temperatures and low pH, which are effective for both enveloped and non-enveloped-lipid viruses (HAV and Parvovirus B19), would theoretically provide an assurance that the viral infectious agents have been removed. Despite the use of those rigorous tests and triple viral inactivation (TVR), as discussed in the Description, a possibility of transmitting infectious agent cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

Some viruses, such as Parvovirus B19 (B19V) or Hepatitis A, are particularly difficult to remove or inactivate. B19V most seriously affects pregnant women, or immunocompromised individuals or those with increased erythropoiesis (e.g. haemolytic anaemia). Symptoms of B19V infection include fever, drowsiness, chills and runny nose followed about two weeks later by rash and joint pain. Evidence of Hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting and abdominal pain. Dark urine and yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

Appropriate vaccinations (hepatitis A and B) should be considered for immune competent patients who receive regular/repeated treatment with KIOVIG.

It is strongly recommended that every time KIOVIG is administered to a patient, the name and batch number of product are recorded in order to maintain a link between the patient and the batch of the product.

Hypersensitivity reactions including anaphylaxis

As with any intravenous product, in particular with a protein substance, allergic type hypersensitivity reactions are possible. Anaphylaxis has been reported with the IV use of KIOVIG and is theoretically possible following SC administration. Prior to commencing subcutaneous therapy, it is recommended that patients should be on stable KIOVIG intravenous therapy that is administered where there are adequate life support facilities and health care professionals prepared to manage anaphylaxis. Patients should be informed of the signs of hypersensitivity reactions including hives, generalised urticaria, and tightness of the chest, wheezing, hypotension and anaphylaxis and trained in the proper recognition and management of these serious reactions. If these symptoms occur, they should be advised to discontinue use of the product immediately, initiate appropriate treatment, and seek urgent medical attention. In the case of anaphylactic shock, the current medical standards for shock treatment should be implemented. Rarely, human normal immunoglobulin can induce an anaphylactic reaction with a fall in blood pressure, even in patients who had tolerated previous treatment with human normal immunoglobulin. Patients with antibodies to IgA may be at increased risk of anaphylactic reaction.

Serious Warning

Immunoglobulin Intravenous (human) products have been reported to be associated with renal adverse reactions including renal dysfunction, acute renal failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, adequate hydration is essential and IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. Formulation of KIOVIG, IgG 10% Solution used Glycine, an amino acid as a stabiliser and it does not contain sucrose. The physician should discuss the risks and benefits of this product with the patient.

Renal Function

Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure.

Assure that patients are not volume depleted prior to the initiation of infusion of KIOVIG. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of IGIV products and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

Severe renal adverse reactions have been reported in patients receiving IV immunoglobulin treatment and are theoretically possible following subcutaneous administration, particularly when using those products containing sucrose (KIOVIG does not contain sucrose). These include acute renal failure (including KIOVIG administered intravenously), acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis.

Haemolysis

KIOVIG contains blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin. These antibodies may cause a positive direct antiglobulin reaction and haemolysis. Acute intravascular haemolysis has been reported, and delayed haemolytic anaemia can develop due to enhanced RBC sequestration. If signs and/or symptoms of haemolysis are present after KIOVIG infusion, appropriate confirmatory laboratory testing should be done.

Thrombotic and Thromboembolic Events

Thrombotic and thromboembolic events have been reported in association with IV immunoglobulin treatment (including KIOVIG administered intravenously), and are possible following subcutaneous administration. These include myocardial infarction, cerebral vascular accident, deep vein thrombosis and pulmonary embolism (see *Adverse Effects*). Thrombotic events have also been reported with

subcutaneous administration of immunoglobulin. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders and prolonged periods of immobilisation. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides).

Aseptic Meningitis Syndrome

An aseptic meningitis syndrome (AMS) has been reported to occur in association with IGIV treatment (including KIOVIG administered intravenously). Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterised by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic mm, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2g/kg) IGIV treatment.

IgA Deficiency

Kiovig is not indicated in patients with IgA deficiency where the IgA deficiency is the only abnormality of concern. These patients should be treated only if their IgA deficiency is associated with an immune deficiency for which therapy with intravenous immunoglobulin is clearly indicated.

Noncardiogenic pulmonary edema

There have been reports of noncardiogenic pulmonary edema (Transfusion Related Acute Lung Injury, TRALI), in patients administered IGIV (including KIOVIG administered intravenously).

Carcinogenicity, Genotoxicity and impairment of fertility

- **Carcinogenicity:** KIOVIG contains a human plasma derived native protein, which is not anticipated to possess carcinogenic potential.
- **Genotoxicity:** KIOVIG contains a human plasma derived native protein, which is not anticipated to possess genotoxic potential.
- **Effects on fertility:** KIOVIG contains a human plasma derived native protein, which is not anticipated to have an adverse effect on fertility.

Use in pregnancy (Category B2)

The safety of KIOVIG for intravenous or subcutaneous 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. Maternally administered IGIV products have been shown to cross the placenta, increasingly during the third trimester. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing KIOVIG.

Use in Lactation

Safety of KIOVIG for use during lactation has not been established. Use of this product in a nursing woman only when is clearly needed and the potential benefit outweigh the potential risks to the baby.

Paediatric Use

The safety and effectiveness of KIOVIG have been established in the age groups 2 to 16. Use of KIOVIG in these age groups is supported by evidence from adequate and well-controlled studies of KIOVIG including paediatric subjects. KIOVIG administered intravenously was evaluated in 15 paediatric subjects with PID (7 were 2 to <12 years old and 8 were 12 to <16) in a multicenter clinical study. KIOVIG administered subcutaneously was evaluated in 18 paediatric subjects with PID (14 were 2 to <12 years old and 4 were 12 to <16) in another multicenter clinical study (see Clinical Trials). There were no differences in the safety and efficacy profiles as compared with adult subjects. No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Safety and efficacy of KIOVIG in paediatric patients below the age of 2 have not been established.

Use in the Elderly

Limited information is available for the geriatric use of KIOVIG. Intravenous administration of KIOVIG was evaluated in 4 subjects over

the age of 65 years, ranging from 67 to 71 years. No overall differences in safety or efficacy were observed for this group. However, caution should be exercised in administering KIOVIG to patients who are at an increased risk for developing renal failure or thromboembolic events. For intravenous administration, infuse KIOVIG at a rate less than 3.3 mg IgG/kg/min (< 2mL/kg/hr) for patients over 65 years of age. Do not exceed the recommended dose, and infuse KIOVIG at the minimum infusion rate practicable. (See *Precautions* and *Dosage and Administration*). Subcutaneous administration of KIOVIG was evaluated in 4 PID subjects over the age of 65 years. No overall differences in safety or efficacy were observed for this group.

Effects on Laboratory Tests

After infusion of IgG, 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, and D) may interfere with some serological tests for red cell antibodies, for example the antiglobulin test (Coombs' test).

INTERACTIONS WITH OTHER MEDICINES

Antibodies in IGIV products may interfere with patient responses to live vaccines, such as those for measles, mumps, rubella and varicella. The immunising physician should be informed of recent therapy with IGIV products so that appropriate precautions can be taken.

Admixtures of KIOVIG with other drugs and intravenous solutions have not been evaluated. It is recommended that KIOVIG be administered separately from other drugs or medications that the patient may be receiving. The product should not be mixed with IGIV products from other manufacturers.

ADVERSE EFFECTS

Intravenous (IV) Administration

Adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time, when they switch from another IGIV brand, or when there has been a long interval since the previous infusion.

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.

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions were pooled from three clinical trials, which consisted of two Primary Immune Deficiency trials (Study #160101 and #160001) and one Idiopathic Thrombocytopenic Purpura trial (Study #160002).

Table 8: Kiovig Liquid Clinical Trial Adverse Reactions

System Organ Class (SOC)	Preferred MedDRA (Version 14.0) Term	Frequency*	Frequency % per Infusion
Infections and Infestations	Meningitis aseptic	Rare	0.09
Blood and Lymphatic System Disorders	Lymphadenopathy	Rare	0.09
	Anaemia	Rare	0.09
Psychiatric Disorders	Anxiety	Rare	0.09
	Insomnia	Rare	0.09
Nervous System Disorders	Migraine	Common	1.36
	Headache	Common	7.10
	Dizziness	Uncommon	0.54
	Dysgeusia	Uncommon	0.18
	Amnesia	Rare	0.09
	Burning sensation	Uncommon	0.09
	Dysarthria	Rare	0.09
Eye Disorders	Eye swelling	Uncommon	0.18
	Eye pain	Uncommon	0.18
	Conjunctivitis	Rare	0.09
Ear and Labyrinth Disorders	Vertigo	Uncommon	0.18
Cardiac Disorders	Tachycardia	Uncommon	0.18
Vascular Disorders	Hypertension	Uncommon	0.27
	Flushing	Uncommon	0.36
	Phlebitis	Rare	0.09
	Peripheral coldness	Rare	0.09
Respiratory, Thoracic and Mediastinal Disorders	Cough	Uncommon	0.36
	Oropharyngeal pain	Uncommon	0.18
	Rhinorrhoea	Rare	0.09
	Oropharyngeal swelling	Rare	0.09
	Asthma	Rare	0.09
	Nasal Congestion	Rare	0.09
Gastrointestinal Disorders	Nausea	Common	8.17
	Diarrhoea	Uncommon	0.36
	Vomiting	Uncommon	0.54
Skin and Subcutaneous Tissue Disorders	Urticaria	Common	1.27
	Pruritus	Uncommon	0.45
	Dermatitis	Rare	0.09
	Rash erythematous	Rare	0.09
	Angioedema	Rare	0.09
	Cold sweat	Rare	0.09
Musculoskeletal and Connective Tissue Disorders	Pain in extremity	Uncommon	0.73
	Back pain	Uncommon	0.36
	Myalgia	Uncommon	0.18
	Muscle spasms	Uncommon	0.18
Injury, Poisoning and Procedural Complications	Contusion	Rare	0.09
General Disorders and Administration Site Conditions	Fatigue	Common	1.91
	Pyrexia	Common	2.32
	Chills	Common	1.27
	Influenza like illness	Uncommon	0.36
	Edema	Uncommon	0.27
	Feeling hot	Uncommon	0.27
	Infusion site phlebitis	Uncommon	0.27
	Infusion site pain	Rare	0.09
	Infusion site swelling	Rare	0.09
	Application site pruritus	Rare	0.09
	Infusion site reaction	Rare	0.09
	Malaise	Rare	0.09
	Investigations	Body temperature increased	Uncommon
Respiratory rate increased		Rare	0.09
White blood cell count decreased		Rare	0.09
Red blood cell count decreased		Rare	0.09
Hematocrit decreased		Rare	0.09
Blood urea increased		Rare	0.09
Blood creatinine increased		Rare	0.09
Blood cholesterol increased		Rare	0.09

* Frequency has been evaluated using the following criteria: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), and very rare (<1/10000).

The following additional adverse reactions were also noted in clinical studies: thyroid disorder, fluid in middle ear, tightness in chest, infection, fungal infection, kidney infection, nasopharyngitis, chronic sinusitis, upper respiratory tract infection and urinary tract infection.

Infusion-Related Adverse Events

Certain adverse reactions such as headache, flushing and changes in pulse rate and blood pressure may occur.

Subcutaneous (SC) Administration

The safety of KIOVIG subcutaneous infusion was evaluated in a prospective, open-label, non-controlled, multi-center clinical study in the 47 subjects who received at least one dose of subcutaneous treatment.

One subject withdrew from the study after 10 treatments with KIOVIG subcutaneous infusion (2.5 months), due to increased fatigue and malaise. No SAEs occurred during subcutaneous treatment.

The most common ADRs with subcutaneous infusion of KIOVIG observed in ≥5% of study subjects in the clinical trial were local infusion site reactions (e.g. swelling, redness, pain), as well as systemic reactions of headache, fever, fatigue, increased heart rate, increased systolic blood pressure, and upper abdominal pain.

Of the 632 non-serious AEs, the most frequent AEs, regardless of causality, and the most frequent temporally associated AEs, which occurred in ≥10% subjects, are shown in Table 9.

Table 9: Adverse Events Irrespective of Causality* in ≥10% of Subjects

Adverse Event	All Adverse Events		Adverse Events* Occurring Within 72 Hours of subcutaneous Infusion	
	Number (%) of Subjects (N= 47)	Number (Rate) of Adverse Events (N= 2294 Infusions)	Number (%) of Subjects (N= 47)	Number (Rate) of Adverse Events (N= 2294 Infusions)
Local Reactions	21 (44.7)	56 (0.028)	21 (44.7)	53 (0.027)
Headache	23 (48.9)	45 (0.020)	18 (38.3)	27 (0.012)
Fever	14 (29.8)	22 (0.010)	9 (19.1)	11 (0.005)
Nausea	8 (17.0)	20 (0.010)	3 (6.4)	6 (0.003)
Vomiting	7 (14.9)	12 (0.005)	5 (10.6)	7 (0.003)
Fatigue	7 (14.9)	11 (0.005)	6 (12.8)	10 (0.004)
Diarrhoea	5 (10.6)	13 (0.006)	3 (6.4)	3 (0.001)
Asthma	6 (12.8)	9 (0.004)	4 (8.5)	6 (0.003)
Oropharyngeal Pain	6 (12.8)	8 (0.003)	3 (6.4)	3 (0.001)
Abdominal Pain Upper	5 (10.6)	12 (0.005)	5 (10.6)	9 (0.004)

* Excluding infections
• Rate per subcutaneous infusions = total number of events divided by total number of subcutaneous infusions

There were 150 AEs considered to be related to KIOVIG use. Of the non-serious AEs related to KIOVIG use, 124 (83%) were mild (transient discomfort that resolves spontaneously or with minimal intervention), 24 (16%) were moderate (limited impairment of function and resolves spontaneously or with minimal intervention with no sequelae), and 2 were severe (marked impairment of function or can lead to temporary inability to resume normal life pattern); requires prolonged intervention or results in sequelae. Neither of the severe AEs required hospitalisation or resulted in sequelae.

The most frequent ADRs (AEs considered by the investigators to be at least possibly related to KIOVIG) that occurred in 5% or more of subjects are shown in Table 10.

Table 10: Related Adverse Reactions* Experienced by ≥5% of Subjects and Rate per Subcutaneous Infusion

Adverse Reaction	Number (%) of Subjects (N= 47)	Number (Rate) of Adverse Reactions (N= 2294 subcutaneous Infusions)
Local Reactions	21 (44.7)	53 (0.027)
Headache	13 (27.7)	20 (0.009)
Fever	6 (12.8)	7 (0.003)
Fatigue	5 (10.6)	8 (0.003)
Heart Rate Increased	3 (6.4)	9 (0.004)
Blood Pressure Systolic Increased	3 (6.4)	6 (0.003)
Abdominal Pain (Upper)	3 (6.4)	4 (0.002)

* Excluding infections
• Rate per subcutaneous infusions= total number of events divided by total number of subcutaneous infusions

Other adverse reactions reported with a frequency < 5% included: abdominal distension, arthralgia, asthma, diastolic blood pressure decreased, blood pressure increased, diarrhoea, ear pain, gravitational edema, haemoglobin decreased, heart rate decreased, malaise, migraine, nausea, peripheral edema, pain in extremity, rash, urticaria and vomiting.

- **Local AEs:** The incidence of local AEs by MedDRA term during all KIOVIG subcutaneous treatment is shown in Table 11.

Table 11: Local Adverse Events (>1 Event)* in All Subjects

Local Adverse Event	Number (Rate) of subcutaneous Infusions			
	Mild	Moderate	Severe	Total
Pain	14 (0.006)	8 (0.003)	0 (0.000)	22 (0.010)
Hematoma	13 (0.006)	1 (<0.001)	0 (0.000)	14 (0.006)
Pruritus	4 (0.002)	2 (0.001)	0 (0.000)	6 (0.003)
Rash	4 (0.002)	0 (0.000)	0 (0.000)	4 (0.002)
Erythema	3 (0.001)	0 (0.000)	0 (0.000)	3 (0.001)
Edema	3 (0.001)	0 (0.000)	0 (0.000)	3 (0.001)
Haemorrhage	2 (0.001)	0 (0.000)	0 (0.000)	2 (0.001)
Irritation	2 (0.001)	0 (0.000)	0 (0.000)	2 (0.001)
Swelling	1 (<0.001)	1 (<0.001)	0 (0.000)	2 (0.001)

* Excluding infections. N=2294 subcutaneous infusions
 • Mild: transient discomfort that resolves spontaneously or with minimal intervention
 • Moderate: limited impairment of function and resolves spontaneously or with minimal intervention with no sequelae
 • Severe: marked impairment of function or can lead to temporary inability to resume normal life pattern; requires prolonged intervention or results in sequelae.

The overall rate of local AEs (excluding infections) during the subcutaneous treatment periods was 2.8% per infusion. In subcutaneous naïve patients, the incidence of local AEs (N=1757 infusions) was 3.3% (2.6% mild and 0.7% moderate with no severe AEs). In the subjects who were subcutaneous experienced (N=537 infusions), the incidence of local AEs was 1.1% (1.1% mild, and no moderate or severe AEs).

In the clinical study after all subcutaneous doses were adjusted, all subjects but one reached the maximum rate allowed in the protocol, 20 mL/site/hour if weight was below 40 kg and 30 mL/hour for weight above 40kg, for one or more of the infusions. 70% (31 of 44) of these subjects opted for the highest rate for all infusions. No subject restricted the rate due to an ADR. In the clinical study, median duration of each weekly infusion was 1.2 hours (range: 0.8–2.3 hours) after all subcutaneous doses were adjusted. The rate set on the pump was that rate per site multiplied by the number of sites, with no maximum.

During all subcutaneous treatment periods, 99.8% of infusions were completed without a reduction, interruption, or discontinuation for tolerability reasons. The proportion of subjects who experienced local AEs (excluding infections) was highest immediately following the switch from intravenous to subcutaneous treatment in all age groups. Over subsequent subcutaneous infusions, there was a decrease of local AEs. The rate of all local AEs per infusion immediately after switching from intravenous to subcutaneous therapy was 4.9% (29/595), decreasing to 1.5% (8/538) by the end of the study and to 1.1% (10/893) in the Study Extension.

Eight (17%) subjects experienced a local adverse reaction during the first infusion, but that decreased to 1 (2.1%) for the subsequent infusions, ranging from 0 to 4 (8.7%) during the first year of subcutaneous therapy. No subject reported a local adverse reaction from week 53 to end of study at week 68.

Post-Marketing Adverse Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These adverse reactions are listed by System Order Class (SOC), then by Preferred MedDRA term in order of severity.

- **Blood and Lymphatic System Disorders:** Haemolysis.
- **Immune System Disorders:** Anaphylactic shock, Anaphylactic reaction, Hypersensitivity.
- **Nervous System Disorders:** Transient ischemic attack, Tremor.
- **Vascular Disorders:** Deep vein thrombosis. Hypotension.
- **Respiratory, Thoracic and Mediastinal Disorders:** Pulmonary embolism, Pulmonary edema, Dyspnea.
- **Gastrointestinal Disorders:** Abdominal pain.
- **Skin and Subcutaneous Tissue Disorders:** Hyperhidrosis.
- **Injury, Poisoning And Procedural Complications:** Transfusion-related acute lung injury.
- **General Disorders and Administration-Site Conditions:** Chest pain, Chills.
- **Investigations:** Coombs' direct test positive, Oxygen saturation decreased.

DOSAGE AND ADMINISTRATION

KIOVIG should be at room temperature during administration. KIOVIG should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter and/or discoloration is observed. Only clear or slightly opalescent and colourless or pale yellow solutions are to be administered. KIOVIG should only be administered intravenously or subcutaneously. Other routes of administration have not been evaluated. The use of an in-line filter is optional.

KIOVIG is recommended for administration by intravenous infusion for all indications. KIOVIG may also be administered subcutaneously for replacement therapy in Primary Immunodeficiency Diseases only (see *Indications*).

For Intravenous (IV) Administration

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 dosage regimens are given as a guideline below.

Recommended Dose and Dosage Adjustment

Dosage will vary depending on condition and bodyweight. The following doses are in agreement with currently suggested dosing schedules (see Table 12).

Table 12: Recommended Dose and Dosage Adjustment

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 symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment	0.2–0.4 g/kg BW	every 3–4 weeks to obtain IgG trough level of at least 4–6 g/L
Immunomodulation:		
Idiopathic thrombocytopenic purpura (ITP)	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 Barre Syndrom (GBS)	0.4 g/kg BW/d	for 3–7 days
Kawasaki disease	1.6–2 g/kg BW or 2 g/kg BW	in several doses in association with acetylsalicylic acid. in one dose in association with acetylsalicylic acid.

As there are significant differences in the half-life of IgG among patients with Primary Immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response. The minimum serum concentration of IgG necessary for protection varies among patients and has not been established by controlled clinical studies.

Rate of Administration

It is recommended that KIOVIG be infused at an initial rate of 0.5 mL/kg/hr. If the infusion at this rate and concentration does not cause the patient to have distress, the administration rate may be gradually increased.

During the first infusion of the Phase 3 clinical study, KIOVIG was infused at an initial rate of 0.5 mL/kg/hr (0.8 mg/kg/min). The rate was gradually increased every 30 minutes to a rate of 5.0 mL/kg/hr (8.9 mg/kg/min) if it was well tolerated. However, some patients completed the infusion before the maximum rate could be obtained.

During subsequent infusions the initial rate and the rate of escalation were based on their previous infusion history; however, the maximum rate attained during the first infusion was used throughout the remainder of the study. A maximum tolerable infusion rate of up to 4 mL/kg/hr was attained in majority (78.7%) of the patients, with a small proportion (19.7%) of patients achieving >4 but <6 mL/kg/hr.

In general, it is recommended that patients beginning treatment with IGIV or switching from one intravenous immunoglobulin (IGIV) 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. It is important to individualise rates for each patient. In patients at risk for acute renal failure or thromboembolic adverse reactions, KIOVIG should not be infused rapidly.

Although there are no prospective studies demonstrating that any concentration or rate of infusion is completely safe, it is believed that

risk is decreased at lower rates of infusion. Therefore, as a guideline, it is recommended that these patients who are judged to be at risk of renal dysfunction or thrombotic complications be gradually titrated up to a more conservative maximal rate of less than 3.3 mg IgG/kg/min (<2mL/kg/hr).

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 Effects*).

Adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time, when they switch from another IGIV brand, or when there has been a long interval since the previous infusion (see *Adverse Effects*).

Trough levels should be measured in order to adjust the dose and dose intervals in particular patients with primary immunodeficiency syndrome. KIOVIG is recommended for infusion at a concentration of 10%. If KIOVIG must be diluted, 5% glucose in water should be used as a diluent. Normal saline should not be used as a diluent though it may be used to flush intravenous lines.

Dilution with 5% glucose solution may result in increased blood glucose levels. This should be taken into account in case of diabetic patients or patients on low sugar diet.

For Subcutaneous (SC) Administration

If self-administration at home or other appropriate setting is planned, the healthcare professional should provide the patient or the carer with adequate training in terms of the correct technique of subcutaneous administration and the correct recognition and management in cases of acute adverse reactions.

For detailed instructions, please refer to the Instruction Leaflet for subcutaneous administration in the package insert.

• SC Dosage:

Prior to switching from intravenous to subcutaneous treatment, obtain the patient's serum IgG trough level to guide subsequent dose adjustments. Start the initial subcutaneous dose approximately one week after the last intravenous infusion in a patient who has been on stable intravenous therapy. Convert the IV dose into weekly equivalents and recheck a serum IgG after several months. The level should be the same or higher than when treated intravenously. Because there is a wide variation in metabolism of IgG between patients with immune deficiency diseases, it is important to individualise dosing. The most important factor when determining dosage of IgG is the clinical response of the patient.

• SC Administration:

Use of an infusion pump and multi-needle administration set is recommended.

Selection of Infusion Site: Suggested areas for subcutaneous infusion of KIOVIG are abdomen, thighs, upper arms, or lower back. Infusion sites should be at least two inches apart, avoiding bony prominences. Rotate sites each week.

Volume per Site: The recommended maximum volume is 30 mL/site for patients above 40 kg (88 lbs) and 20 mL/site for patients under 40 kg (88 lbs). The weekly dose (mL) should be divided by 30 or 20, based on patient weight above, to determine the number of sites required. Simultaneous subcutaneous infusion at multiple sites can be facilitated by use of a multi-needle administration set.

Rate of Infusion. Patients over 40 kg (88 lbs): For the first infusion, the recommended maximum rate of infusion of KIOVIG is 20mL/hr/site. For subsequent infusions, the flow rate should be adjusted as tolerated to a maximum of 30 mL/hr/site. If multiple sites are used, the rate set on the pump should be the rate per site multiplied by the number of sites (e.g., 30 mL x 4 sites = 120 mL/hr). The number of simultaneous sites should be limited to 8, or maximum infusion rate of 240 mL/hr.

Patients under 40 kg (88 lbs): For the first infusion, the recommended maximum rate of infusion of KIOVIG is 15mL/hr/site. For subsequent infusions, the flow rate should be adjusted as tolerated to a maximum of 20 mL/hr/site. If multiple sites are used, the rate set on the pump should be the rate per site multiplied by the number of sites (e.g., 20 mL x 3 sites = 60 mL/hr). The number of simultaneous sites should be limited to 8, or maximum infusion rate of 160 mL/hr.

OVERDOSAGE

With intravenous administration, overdose may lead to fluid overload and hyperviscosity. Patients at particular risk of complications of fluid

overload and hyperviscosity include elderly patients and patients with cardiac or renal impairment.

Contact the Poisons Information Centre (telephone: 13 11 26) for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Nature and Contents of Container

KIOVIG is available in several sizes: 1g/10mL, 2.5g/25mL, 5g/50mL, 10g/100mL, and 20g/200 mL. The product is filled into glass containers of type I, which are closed with bromobutyl rubber stoppers.

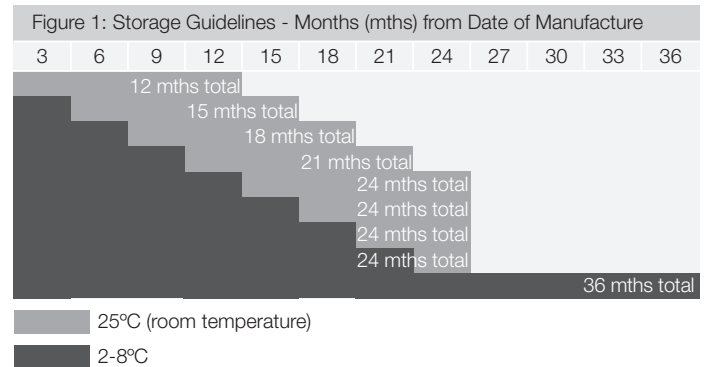
Shelf life

36 months

Special Precautions for Storage

- At 2°C to 8°C (Refrigerate. Do not Freeze) for the duration of the shelf life.
- At room temperature: KIOVIG may be stored at room temperature (below 25°C) for up to 12 months within the first 24 months. However, once stored at room temperature, the product must remain stored at room temperature and must be used within the first 24 months from the date of manufacture.

The total storage time of KIOVIG depends on the point of time the vial is transferred to room temperature. Examples for total storage times are illustrated in Figure 1. The new expiration date must be recorded on the package when the product is transferred to room temperature. Product cannot be stored at room temperature after 24 months from date of manufacture.



- Example 1: If the product is taken out of the refrigerator after 3 months, it can be stored for 12 months at room temperature, and the total storage time is 15 months.
- Example 2: if the product is taken out of the refrigerator after 15 months, it can be stored for 9 months at room temperature, and the total storage time is 24 months. Once the product has been stored at room temperature, the product should not be re-refrigerated.

Do not use after the expiry date stated on the label.

Keep the container in the outer carton in order to protect from light. In the case of the product is diluted, the preparation should be used as soon as practicable, in order to reduce microbiological hazard, as the product does not contain antimicrobial preservative. If storage is necessary, store the diluted preparation at 2°C to 8°C for not more than 24 hours. Product is for a single use in one patient only.

Discard any residue.

Baxter

NAME AND ADDRESS OF THE SPONSOR

KIOVIG is manufactured by:

Baxter AG, Industriestrasse 67
A-1221 Vienna Austria.

Distributed in Australia by:

Baxter Healthcare Pty Ltd
1 Baxter Drive, Old Toongabbie, NSW 2146

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG) 02 September 2008

DATE OF MOST RECENT AMENDMENT 30 November 2011

Kiovig 10% will be funded and supplied under the national blood arrangements only as an IVlg product at this time.

PA041B/2011