AUSTRALIAN PRODUCT INFORMATION

KIOVIG® (Normal immunoglobulin (Human))

1 NAME OF THE MEDICINE

Normal Immunoglobulin (Human).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KIOVIG vials contain 1.0 g in 10 mL, 2.5 g in 25 mL, 5.0 g in 50 mL, 10.0 g in 100 mL, 20.0 g in 200 mL or 30.0 g in 300 mL of the active normal immunoglobulin (Human) [Immunoglobulin G (IgG) 100 mg/mL].

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

Description

The active ingredient in KIOVIG is a human plasma-derived immunoglobulin, concentration of 100 mg/mL (10% w/v), produced from large pools of human plasma by a modified Cohn-Oncley cold ethanol fractionation, yielding an intermediate immunoglobulin G (IgG), 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 (30ºC to 32 ºC, pasteurisation for 21 to 23 days) has been 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 IgG1 ≥ 56.9%, IgG2 ≥ 26.6 %, IgG3 ≥ 3.4%, and 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 a reduction in the incidence of infusion-related adverse reactions. It contains glycine which acts as a stabilising agent for the proteins. The product does not contain preservative.

3 PHARMACEUTICAL FORM

Solution for intravenous and subcutaneous injection.

Appearance

The solution is clear or slightly opalescent and colourless.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

KIOVIG administered intravenously is indicated for:

1. *Replacement therapy indications*
   - Primary immunodeficiency disorders (PID);
   - Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

2. *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;
   - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in adults.
   - Multifocal Motor Neuropathy (MMN).

KIOVIG administered subcutaneously is indicated for:

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

4.2 DOSE AND METHOD OF 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 PID only (see Section 4.1 THERAPEUTIC INDICATIONS).

See Section 4.4 Special Warnings and Precautions for Use about interchangeability of IVIGs.

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 1).

Table 1 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 Barré Syndrome (GBS)	0.4 g/kg BW/d	For 3 - 7 days
- Kawasaki disease	1.6 – 2 g/kg BW Or: 2 g/kg BW Starting dose:	In several doses in association with acetylsalicylic acid. In one dose in association with acetylsalicylic acid In divided doses over 2 – 5 days

Table 1 Recommended Dose and Dosage Adjustment

Indication	Dose	Frequency of Injections
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)*	2 g/kg Maintenance dose: 1 g/kg	Over 1 – 2 consecutive days over 3 weeks
- Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 0.4 - 2 g/kg	In divided doses over 2 - 5 days Every 2 - 6 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 physician's 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.

As there are significant differences in the half-life of IgG among patients with PID, 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.

Dose adjustments for IV administration in MMN

Intravenous immunoglobulin (IVIG) should be used for three to six months (three to six courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary. If there is no benefit after three to six courses, IVIG therapy should be abandoned.

Regular review by neurologist is required: frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Rate of administration

It is recommended that KIOVIG be infused at an initial rate of 0.5 mL/kg/h. 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/h (0.8 mg/kg/min). The rate was gradually increased every 30 minutes to a rate of 5.0 mL/kg/h (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/h was attained in majority (78.7%) of the patients, with a small proportion (19.7%) of patients achieving > 4 but < 6 mL/kg/h.

In general, it is recommended that patients beginning treatment with IVIG or switching from one 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. 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/h).

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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Adverse reactions may occur more frequently in 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

Subcutaneous 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 intravenous dose into weekly equivalents and recheck the serum IgG trough level 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.

Subcutaneous Administration

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

Selection of Infusion Site

Volume per Site: The recommended maximum volume is 30 mL/site for patients above 40 kg and 20 mL/site for patients under 40 kg. 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: For the first infusion, the recommended maximum rate of infusion of KIOVIG is 20mL/h/site. For subsequent infusions, the flow rate should be adjusted as tolerated to a maximum of 30 mL/h/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/h). The number of simultaneous sites should be limited to 8, or maximum infusion rate of 240 mL/h.

Patients under 40 kg (88 lbs): For the first infusion, the recommended maximum rate of infusion of KIOVIG is 15mL/h/site. For subsequent infusions, the flow rate should be adjusted as tolerated to a maximum of 20 mL/h/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/h). The number of simultaneous sites should be limited to 8, or maximum infusion rate of 160 mL/h.

4.3 CONTRAINDICATIONS

KIOVIG, IgG 10% solution is contraindicated in patients with known anaphylactic or severe hypersensitivity responses to normal immunoglobulin (human). Patients with severe selective Immunoglobulin A (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 37 μg/mL). These patients should be treated only if their IgA deficiency is associated with an immune deficiency for which therapy with IVIG is clearly indicated. Such patients should only receive IVIG with utmost caution and in a setting where supportive care is available for treating life-threatening reactions.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infusions of immunoglobulin 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 (1-2 g/kg) doses of IgG. Risk can be reduced by ensuring adequate hydration before administration 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 IVIG products.

Intravenous infusions of IVIG have been associated with an aseptic meningitis syndrome (AMS) with severe headache, nuchal rigidity, cerebro-spinal fluid (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 (1-2 g/kg) doses of IVIG 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 subcutaneous infusions not be given to patients with ITP due to the increased risk of bleeding and hematoma.

While IVIGs are interchangeable, they are not therapeutically equivalent in terms of efficacy and safety profiles.

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The recommended infusion rate given under “Dosage and Administration” must be closely followed.

Potential complications can often be avoided by ensuring that patients are carefully monitored for any symptoms throughout the infusion period. Patients naive to human normal

immunoglobulin, patients switched from an alternative product to KIOVIG, 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. 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; and
- 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 IVIG 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 centres 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 nano-filtration 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 Parvovirus B19 (B19V) or Hepatitis A (HAV), are particularly difficult to remove or inactivate. B19V most seriously affects pregnant women, or immune-compromised 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 HAV 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 products 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 intravenous use of KIOVIG and is theoretically possible following subcutaneous 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

Intravenously administered normal immunoglobulin (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 IVIG 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 IVIG products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number.

Formulation of KIOVIG, IgG 10% solution uses 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 IVIG 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 IVIG 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 that may act as haemolysins and induce *in vivo* coating of red blood cells (RBC) with immune globulin. This may cause a positive direct antiglobulin test (DAT) (Coombs' test). Delayed haemolytic anaemia can develop subsequent

to KIOVIG therapy due to enhanced RBC sequestration; acute haemolysis, consistent with intravascular haemolysis, has been reported.

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.

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 IVIG 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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, obesity, diabetes mellitus, acquired or inherited thrombophilic disorder, a history of vascular disease and a history of a previous thrombotic or thromboembolic event. The potential risks and benefits of IVIG should be weighed against those of alternative therapies for all patients for whom IVIG 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 immunoglobulin treatment (including KIOVIG administered intravenously). Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IVIG 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 (2 g/kg) IVIG treatment.

AMS may occur more frequently in female patients.

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 oedema

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

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 multicentre 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 multicentre clinical study (See Section 5.1 PHARMACODYNAMIC PROPERTIES/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.
The use of KIOVIG in the treatment of CIDP in the paediatric population has 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF 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 DAT (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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Antibodies in IVIG 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 IVIG 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 IVIG products from other manufacturers.

4.6 FERTILITY, PREGNANCY AND LACTATION

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.

There are no adequate data from the use of KIOVIG in pregnant women.

Maternally administered IVIG products have been shown to cross the placenta, increasingly during the third trimester. Physicians should balance the potential risks and only prescribe KIOVIG if clearly needed.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 IVIG 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 from KIOVIG clinical trials (Studies 160001, 160002, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160604, 160902, 160701, 161003, 161202) are shown in Table 2:

Table 2 ADRs in Clinical Trials Across All Indications [N=687] (Studies 160001, 160002, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160604, 160902, 160701, 161003, 161202)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=687)	Frequency Category
INFECTIONS AND INFESTATIONS	Aseptic meningitis	0.1	Uncommon
BLOOD AND LYMPHATIC DISORDERS	Anaemia	2.3	Common
	Lymphadenopathy	1.3	Common
IMMUNE SYSTEM DISORDERS	Hypersensitivity	0.6	Uncommon
	Anaphylactic reaction	0.3	Uncommon

Table 2 ADRs in Clinical Trials Across All Indications [N=687] (Studies 160001, 160002, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160604, 160902, 160701, 161003, 161202)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=687)	Frequency Category
METABOLISM AND NUTRITION DISORDERS	Decreased appetite	1.7	Common
PSYCHIATRIC DISORDERS	Anxiety	4.8	Common
	Irritability	1.2	Common
	Insomnia	2.9	Common
NERVOUS SYSTEM DISORDER	Headache	28.8	Very Common
	Dizziness	7.6	Common
	Migraine	1.7	Common
	Paraesthesia	1.2	Common
	Dysgeusia	0.4	Uncommon
	Balance disorder	0.4	Uncommon
	Dysarthria	0.1	Uncommon
	Hypoesthesia	0.6	Uncommon
	Amnesia	0.1	Uncommon
EYE DISORDERS	Conjunctivitis	1.3	Common
	Eye swelling	0.3	Uncommon
	Eye pain	0.1	Uncommon
EAR AND LABYRINTH DISORDERS	Vertigo	0.7	Uncommon
CARDIAC DISORDERS	Tachycardia (including sinus tachycardia)	1.7	Common
VASCULAR DISORDERS	Hypertension (including blood pressure increased)	12.5	Very Common
	Flushing (including hot flush)	2.5	Common
	Phlebitis	0.6	Uncommon
	Peripheral coldness	0.4	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough	7.0	Common
	Nasal congestion	2.9	Common
	Rhinorrhoea	2.5	Common
	Oropharyngeal pain	2.3	Common
	Dyspnoea	1.5	Common
	Pulmonary embolism	0.4	Uncommon
	Oropharyngeal swelling	0.1	Uncommon
GASTROINTESTINAL DISORDERS	Nausea	10.2	Very Common
	Diarrhoea	9.5	Common
	Vomiting	7.7	Common
	Abdominal pain (including abdominal pain upper, lower and tenderness)	4.1	Common
	Dyspepsia	1.3	Common
	Abdominal distension	0.9	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash (including erythematous, pruritic, maculo-papular, papular)	11.8	Very Common
	Contusion	5.2	Common
	Urticaria	2.5	Common
	Pruritus	2.5	Common
	Dermatitis	1.2	Common
	Erythema	1.0	Common
	Night sweats	0.6	Uncommon
	Photosensitivity reaction	0.1	Uncommon
	Cold sweat	0.3	Uncommon
	Angioedema	0.1	Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Back pain	7.7	Common
	Arthralgia	5.5	Common
	Pain in extremity	6.1	Common
	Muscle spasms	3.6	Common

Table 2 ADRs in Clinical Trials Across All Indications [N=687] (Studies 160001, 160002, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160604, 160902, 160701, 161003, 161202)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=687)	Frequency Category
	Myalgia	3.1	Common
	Muscular weakness	1.7	Common
	Muscle twitching	0.1	Uncommon
RENAL AND URINARY DISORDERS	Proteinuria	0.3	Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Local reactions	13.1	Very Common
	• Infusion site extravasation	7.9	Common
	• Infusion site pain (including Discomfort)	1.9	Common
		1.0	Common
	• Infusion site swelling (including Local swelling, Local oedema)	0.1	Uncommon
	• Infusion site pruritus		
	Fatigue (including Lethargy)	11.1	Very Common
	Pyrexia (including Body temperature increased)	10.0	Very Common
	Chills	7.4	Common
	Oedema (including peripheral, Swelling)	4.1	Common
	Influenza like illness	1.9	Common
	Malaise	1.5	Common
	Chest discomfort	1.3	Common
	Chest tightness	0.3	Uncommon
	Feeling hot	0.3	Uncommon
	Burning sensation	0.1	Uncommon
INVESTIGATIONS	Blood urea increased	0.6	Uncommon
	White blood cell count decreased	0.6	Uncommon
	Alanine aminotransferase increased	0.4	Uncommon
	Haematocrit decreased	0.4	Uncommon
	Red blood cell count decreased	0.4	Uncommon
	Blood creatinine increased	0.3	Uncommon
	Respiratory rate increased	0.1	Uncommon
	Blood cholesterol increased	0.6	Uncommon

Legend:
ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000).

Primary immune deficiency

Two serious adverse events were reported in the PID clinical trials, 2 episodes of aseptic meningitis in one patient. It is not possible to come to any conclusions regarding risk factors by indication, dose, or individual patient characteristics.

Table 3 PID Clinical Trial ADRs [N=189] (160001, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160902)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=189)	Frequency Category
INFECTIONS AND INFESTATIONS	Aseptic meningitis	0.5	Uncommon
BLOOD AND LYMPHATIC DISORDERS	Lymphadenopathy	3.7	Common
	Anaemia	1.6	Common
IMMUNE SYSTEM DISORDERS	Anaphylactic reaction	0.5	Uncommon
NERVOUS SYSTEM DISORDERS	Headache	47.1	Very Common
	Migraine	5.8	Common

Table 3 PID Clinical Trial ADRs [N=189] (160001, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160902)

	Dizziness	7.9	Common
	Dysgeusia	0.5	Uncommon
	Amnesia	0.5	Uncommon
	Dysarthria	0.5	Uncommon
EYE DISORDERS	Conjunctivitis	4.2	Common
	Eye pain	0.5	Uncommon
	Eye swelling	0.5	Uncommon
EAR AND LABYRINTH DISORDERS	Vertigo	1.1	Common
CARDIAC DISORDERS	Tachycardia	3.7	Common
VASCULAR DISORDERS	Flushing	2.1	Common
	Hypertension	1.6	Common
	Peripheral coldness	0.5	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough	11.6	Very Common
	Pharyngolaryngeal pain	7.4	Common
	Nasal congestion	6.3	Common
	Rhinorrhoea	4.2	Common
	Dyspnoea	2.6	Common
	Oropharyngeal swelling	0.5	Uncommon
GASTROINTESTINAL DISORDERS	Nausea	14.3	Very Common
	Vomiting	13.2	Very Common
	Diarrhoea	11.1	Very Common
	Abdominal pain	8.5	Common
	Dyspepsia	1.6	Common
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Urticaria	4.2	Common
	Pruritus	5.3	Common
	Rash	5.8	Common
	Contusion	3.7	Common
	Angioedema	0.5	Uncommon
	Cold sweat	0.5	Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	7.9	Common
	Pain in extremity	10.1	Very Common
	Back pain	7.4	Common
	Myalgia	6.3	Common
	Muscle spasms	1.6	Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Local reactions	6.9	Common
	Infusion site pain	2.1	Common
	Infusion site swelling	1.1	Common
	Fatigue	15.3	Very Common
	Pyrexia	20.1	Very Common
	Chills	9.5	Common
	Oedema	4.8	Common
	Influenza like illness	2.1	Common
	Malaise	2.6	Common
	Chest tightness	1.1	Common
	Feeling hot	0.5	Uncommon
INVESTIGATIONS	White blood cell count decreased	1.6	Common
	Blood creatinine increased	1.1	Common
	Blood urea increased	1.1	Common
	Hematocrit decreased	0.5	Uncommon
	Red blood cell count decreased	0.5	Uncommon
	Respiratory rate increased	0.5	Uncommon

Legend:
ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000).

Idiopathic thrombocytopenic purpura (ITP)

Headache was reported more frequently in ITP patients than in PID or MMN, however, no patients in the ITP study reported migraine, which occurred commonly in the other patient populations. Muscle spasms and pain in extremity were common for patients with ITP but uncommon for other indications.

Table 4 ITP Clinical Trial ADRs [N=23] (160002)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=23)	Frequency Category
PSYCHIATRIC DISORDERS	Anxiety	4.3	Common
NERVOUS SYSTEM DISORDERS	Headache	34.8	Very Common
	Insomnia	4.3	Common
VASCULAR DISORDERS	Hypertension	17.4	Very Common
	Flushing	4.3	Common
	Phlebitis	4.3	Common
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Rhinorrhoea	4.3	Common
GASTROINTESTINAL DISORDERS	Nausea	13.0	Very Common
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dermatitis	4.3	Common
	Rash	4.3	Common
	Urticaria	4.3	Common
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Pain in extremity	4.3	Common
	Back pain	4.3	Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia (including Body temperature increased)	47.8	Very Common
	Local reactions	4.3	Common
	Infusion site pain	4.3	Common

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000).

Multifocal motor neuropathy (MMN)

One serious adverse event, pulmonary embolism, was reported in the MMN clinical trial. Due to the low incidence of pulmonary embolism, it is not possible to come to any conclusions regarding risk factors by indication, dose, or individual patient characteristics.

Muscle twitching and weakness were reported only in patients with MMN and may also be related to their underlying neuromuscular condition.

Table 5 MMN Clinical Trial ADRs [N=44] (160604)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=44)	Frequency Category
NERVOUS SYSTEM DISORDERS	Headache	36.4	Very Common
	Paraesthesia	6.8	Common
	Balance disorder	2.3	Common
	Migraine	2.3	Common
CARDIAC DISORDERS	Tachycardia	2.3	Common
VASCULAR DISORDERS	Flushing	6.8	Common
	Hypertension	6.8	Common
	Phlebitis	2.3	Common
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Oropharyngeal pain	15.9	Very Common
	Pulmonary embolism	2.3	Common
	Nausea	6.8	Common

Table 5 MMN Clinical Trial ADRs [N=44] (160604)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=44)	Frequency Category
GASTROINTESTINAL DISORDERS	Vomiting	2.3	Common
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Photosensitivity reaction	2.3	Common
	Night sweats	2.3	Common
	Rash	2.3	Common
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Muscular weakness	13.6	Very Common
	Pain in extremity	9.1	Common
	Back pain	11.4	Very Common
	Myalgia	4.5	Common
	Muscle twitching	2.3	Common
RENAL AND URINARY DISORDERS	Proteinuria	2.3	Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Influenza like illness	15.9	Very Common
	Fatigue	6.8	Common
	Local reactions	13.6	Very Common
	Chest discomfort	6.8	Common
	Oedema	4.5	Common
	Pyrexia	4.5	Common
	Chills	2.3	Common
INVESTIGATIONS	Alanine aminotransferase increased	2.3	Common

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common ≥ 1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000).

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-centre 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 serious adverse events (SAEs) occurred during subcutaneous treatment.

The most common adverse drug reactions (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 adverse events (AEs), the most frequent AEs, regardless of causality, and the most frequent temporally associated AEs, which occurred in ≥10% subjects.

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.

Table 6 Subcutaneous Clinical Trial ADRs [N=47] (160601)

System Organ Class	Preferred MedDRA Term (Version 17.0)	By Subject % (N=47)	Frequency Category
NERVOUS SYSTEM DISORDERS	Headache	48.9	Very Common
CARDIAC DISORDERS	Tachycardia	6.4	Common
GASTROINTESTINAL DISORDERS	Vomiting	14.9	Very Common
	Nausea	17.0	Very Common
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Back pain	4.3	Common
	Arthralgia	6.4	Common
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Local reactions	40.4	Very Common
	Pyrexia	29.8	Very Common

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000).

Local adverse events

The incidence of local AEs by MedDRA term during all KIOVIG subcutaneous treatment is shown in Table 7.

Table 7 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)
OEDEMA	3 (0.001)	0 (0.000)	0 (0.000)	3 (0.001)
HEMORRHAGE	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 40 kg, 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.

Intravenous administration

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Haemolysis.

IMMUNE SYSTEM DISORDERS: Anaphylactic shock, anaphylactic reaction, hypersensitivity.

NERVOUS SYSTEM DISORDERS: Cerebral vascular accident, transient ischemic attack, tremor.

CARDIAC DISORDERS: Myocardial infarction.

VASCULAR DISORDERS: Myocardial Infarction, deep vein thrombosis, hypotension.

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Pulmonary embolism, pulmonary oedema, dyspnoea.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Hyperhidrosis, exfoliative dermatitis.

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.

Subcutaneous Administration

IMMUNE SYSTEM DISORDERS: Hypersensitivity.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Myalgia.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Chills.

Class reactions

Subcutaneous Administration

Post-marketing ADRs have not been reported with KIOVIG administered subcutaneously. However, the following additional ADRs have been identified and reported during the post-marketing use of another subcutaneous immune globulin product: Anaphylactic reaction, paraesthesia, tremor, tachycardia, hypotension, Dyspnoea, laryngospasm, chest discomfort, injections site reaction (including induration, warmth).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report ant suspected adverse reaction at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 intravenous immunoglobulin (IVIG) 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 ingredient in KIOVIG, IgG 10% w/v, is a plasma-derived immunoglobulin isolated from a pooled 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 IgG levels of immune deficient patients to a normal range.

Clinical trials

Clinical Studies of Intravenous (IV) Administration

Efficacy and safety of KIOVIG, 10% IVIG solution, was assessed in three clinical studies, a European study in 22 patients with hypo- or agammaglobulinemia, a US study in 61 patients with PID, and a European study in 23 patients with idiopathic thrombocytopenia purpura (ITP). None of these studies were designed to compare KIOVIG with another IVIG product.

The use of KIOVIG, 10 % IVIG solution in patients with PID 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 8.

Table 8 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	Randomised, double-blinded, uncontrolled, multicentre	300 – 600mg/kg BW* every 21 – 28 days; IV 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

*BW=Body Weight.

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 (see Table 9).

Table 9 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
Hospitalisations Secondary to Infection	0
Mean Number of Validated Infections per Subject per year	0
p-value[b]	p< 0.0001
95% Confidence Interval[b]	(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 10). 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 10 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

[a]Other bacterial infections that met specific diagnostic requirements.

Table 10 Summary of Validated Other Bacterial Infections

	Number of events
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)

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 common infections in this patient population (sinusitis, bronchitis, nasopharyngitis, urinary tract infections, and upper respiratory infections).

Multifocal Motor Neuropathy (MMN)

A randomised withdrawal, double-blind, placebo controlled, cross-over Study 160604 was conducted to evaluate the efficacy and safety/tolerability of KIOVIG in 44 adult subjects with MMN. The study examined grip strength in the more affected hand (measured with dynamometer), and Guy's Neurological Disability Scale (GNDS) [upper limb part 6 subsection].

The median monthly dose of IVIG, 10% administered was 1.2 g/kg BW (range: 0.5 to 2.4). Subjects were treated at infusion cycles of 2, 3 or 4 weeks, the dose for each infusion cycle being administered either in a single infusion or divided over a maximum of 5 consecutive days.

Study subjects were on a regimen of licensed immunoglobulin (existing maintenance dose ranging from 0.5 to 2.0 grams/kg/month) prior to enrolment. The clinical trial was an enrichment design; therefore, the results cannot be generalised to naïve patients. Each subject completed a five part, 12-week study (3 stabilisation phases, one randomised withdrawal and one cross-over period). If, during the double-blinded treatment period, the subject's upper limb function involving the affected muscles deteriorated, such that the subject had difficulty completing daily activities or the subject experienced a decline in grip strength of ≥50% in the more affected hand, the subject was switched directly to the next stabilisation phase of open-label KIOVIG ("accelerated switch") without breaking the blind.

All subjects were treated for 12 weeks with KIOVIG during the initial stabilisation (Stabilisation-1) phase. In the cross-over 1 period, each subject was then randomised to either withdrawal from KIOVIG to placebo or continue KIOVIG for a period of 12 weeks and then transferred to stabilisation phase 2. Subjects that did not tolerate the treatment during the double-blind cross-over period were immediately transferred to open label KIOVIG stabilisation phase 2.

Following stabilisation phase 2, the subjects were assigned to a second double-blind treatment for 12 weeks to either placebo or KIOVIG depending on randomisation received in cross-over period 1. No subject was allowed to experience placebo more than one time during the clinical study. Following this period, the subjects were further stabilised for 12 weeks on open-label KIOVIG, stabilisation phase 3.

Sixty nine percent (n=29) required an accelerated switch to open-label treatment with KIOVIG during the placebo period due to functional deterioration but did not switch when receiving KIOVIG. The median treatment days for treatment with KIOVIG was 84 days and the median treatment days for the placebo was 28 days. Only one subject (2.4%) switched to open-label treatment during blinded KIOVIG cross-over period 1 but did not switch during placebo administration ($p < 0.001$).

Forty-four subjects were evaluated to demonstrate effectiveness of KIOVIG to improve or maintain muscle strength and functional ability in patients with MMN.
Statistical significance in favour of KIOVIG over placebo was demonstrated by a substantially lower decline from baseline (22.30%; 95% CI: 9.92% to 34.67%) in the mean

grip strength in the more affected hand following treatment (see Table 11). The difference in relative change for KIOVIG and placebo of 22.94% (95% CI: 10.69 to 35.19) was statistically significant (p <0.001).

Table 11 Relative Change in Grip Strength in the More Affected Hand During Cross-Over Period (ANOVA) (Intent-to-Treat Dataset) No. of Subjects (N=41)

Statistics	Sequence 1		Sequence 2		Difference
	KIOVIG	Placebo	Placebo	KIOVIG	(KIOVIG – Placebo)
N	22	22	19	20*	41
Mean (SD)	-16.36 (32.84)	-30.52 (29.68)	-29.19 (39.95)	1.46 (10.72)	22.30 (39.21)
Median	-3.90	-27.00	-25.03	-0.11	26.6

*A single subject in sequence 2, who was considered an outlier, was excluded from analysis.

Guy's Neurological Disability Scores (GNDS) for the upper limbs, reflecting both fine motor skills and proximal strength, showed a significant difference in efficacy between KIOVIG and placebo at the 2.5% level in favour of KIOVIG. GNDS is a patient orientated clinical disability scale designed for multiple sclerosis and is considered appropriate for other neurological disorders.

As determined by GNDS scores for the upper limbs, 35.7% of subjects deteriorated while receiving the placebo, but not during treatment with KIOVIG whereas 11.9% of subjects deteriorated during KIOVIG but not over the placebo period. This difference was statistically significant (p=0.021) (see Table 12). 4.8% of subjects showed deterioration with both placebo and KIOVIG, while 47.6% showed no deterioration on either.

Table 12 McNemar's Test for Subjects with Deterioration in Guy's Neurological Disability Score

(Intent-to-Treat Dataset) No. of Subjects (N=42)	
Deterioration on placebo	15 (35.7%)
Deterioration on KIOVIG	5 (11.9%)
Deterioration on both	2 (4.8%)
No deterioration	20 (47.6%)

When data from both treatment sequences were combined, a relative decline of ≥30% in grip strength in the more affected hand occurred in 42.9% of subjects during the placebo period, but not during treatment with KIOVIG. 4.8% of subjects experienced a ≥30% decline during treatment with KIOVIG, but not during placebo. A relative decline of ≥30% in grip strength in the less affected hand occurred in 31.0% of subjects during the placebo period, but not during treatment with KIOVIG. No subject experienced a ≥30% decline during treatment with KIOVIG.

The Overall Disability Sum Score (ODSS) changed by -7.14% during placebo (indicating worsening of disability), and by -1.11% (indicating no change in disability) during treatment with KIOVIG.

At the end of the placebo period, subjects required 17% longer to complete the 9-hole peg test (a measure of dexterity) with the dominant hand, and 33% longer with the non-dominant hand, compared to baseline. During KIOVIG treatment, dexterity increased by a mean of 1.2% compared to baseline in the dominant hand and 6.7% in the non-dominant hand.

Compared to baseline, patients' assessment of physical functioning, as measured by visual analogue scale (VAS), showed a mean change of 290% during placebo compared to baseline. Patient's assessments of physical functioning showed a mean change of 73% during KIOVIG treatment. Higher visual analogue scale scores represent more severe disability.

Clinical Study of Subcutaneous (SC) Administratio

A prospective, open-label, non-randomised, multi-centre 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 13. 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 13 Summary of Infections and Associated Events

Number of subjects (efficacy phase) Total number of subject years Annual rate of any infections	47 44 4.1 (95% CI 3.2 to 5.1) infections/subject year
Antibiotic use[§] (prophylaxis or treatment) Number of subjects (%) Annual rate	 40 (85.1%) 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 (%) Annual rate	 25 (53.2%) 4.0 (95% CI 2.5 to 6.1) days/subject year
Hospitalisations due to infections Number of subjects (%) Annual rate	 0 (0.0%) 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.

5.2 PHARMACOKINETIC PROPERTIES

Intravenous administration

Normal immunoglobulin (Human) 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-centre 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 KIOVIG 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 to be 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 14. 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 PID. The values obtained are comparable to parameters reported for other human immunoglobulins.

Table 14 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
C_{min} (mg/dL) (trough level)	22	848	772 : 1000
C_{max} (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
T_{max} (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 PID who were 12 years and older during a clinical study (see Section 5.1 PHARMACODYNAMIC PROPERTIES/Clinical trials/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 to 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 16. 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 15 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

KIOVIG contains a human plasma derived native protein, which is not anticipated to possess genotoxic potential.

Carcinogenicity

KIOVIG contains a human plasma derived native protein, which is not anticipated to possess carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

KIOVIG contains the following excipients:

- Glycine.
- Water for injection.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf-life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C for up to 36 months from date of manufacture. Refrigerate. Do not freeze. The product may be stored at room temperature not exceeding 25°C for up to 3 months. Once stored at room temperature, do not return it to the refrigerator. Discard after 3 months at room temperature.

Do not use after the expiry date. Protect from light.

If KIOVIG is diluted, the preparation should be used as soon as practicable 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.

6.5 NATURE AND CONTENTS OF CONTAINER

KIOVIG is available in several sizes: 1g/10mL, 2.5g/25mL, 5g/50mL, 10g/100mL, 20g/200 mL and 30g/300mL. The product is filled into glass containers of type I, which are closed with bromobutyl rubber stoppers.

Pack size

1 vial per carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name

Normal Immunoglobulin (human).

Chemical structures

The active ingredient in KIOVIG is normal immunoglobulin (human) comprising predominantly of polyvalent IgG. Immunoglobulins are made up of four polypeptide chains, comprising two identical light chains of a molecular weight of approximately 25 kD and two identical heavy chain of molecular weight of approximately 50 kD. 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 150 kD.

Immunoglobulin G antibodies are the most common immunoglobulin class, with a level of 9 - 12 grams 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.

CAS number

Normal immunoglobulin 10% (Human): not available.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

1g, 2.5g, 5g, 10g, 20g: 02 September 2008

30g: 29 May 2013

10 DATE OF REVISION

07 August 2026

Summary table of changes

Section Changed	Summary of new information
6.4	Addition of room temperature storage condition

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