INTRAGAM® P

Human Normal Immunoglobulin, solution for intravenous injection

Product Information

Australia

NAME OF THE MEDICINE
Human Normal Immunoglobulin solution for intravenous injection.

DESCRIPTION
Intragam® P is a sterile, preservative free solution containing 6 g of human protein and 10 g of maltose in each 100 mL.

The solution has a pH of 4.25. Ionotoxicity is achieved by the addition of maltose. At least 98% of the protein has the electrophoretic mobility of immunoglobulin G (IgG). At least 90% of the protein is IgG monomer and dimer. Based on three preclinical and four clinical batches, the distribution of IgG subclasses present in Intragam® P is, on the average, 61% IgG1, 36% IgG2, 3% IgG3, and 1% IgG4. Intragam® P contains only trace amounts of IgA (normally < 0.025mg/mL). Intragam® P is intended for intravenous administration.

Intragam® P is made by chromatographic fractionation of large fractions of human plasma obtained from voluntary blood donors. The protein has not been chemically or enzymatically modified. The manufacturing process contains specific steps to reduce the possibility of virus transmission including pasteurisation (heating at 52°C for 30 minutes) and irradiation at low pH.

PHARMACOLOGY AND PHARMACOKINETICS
The steady-state kinetic parameters for serum IgG were determined in 11 patients (9 male, age 28-76 years) with primary immunodeficiency disorders, following the administration of monthly intravenous infusions of Intragam® P for six months. The dose of Intragam® P was individualised in the range 0.35 to 0.53 g/kg. The mean serum IgG concentration ranged from a trough of 7.4±1.1 g/L to a peak of 15.8±1.7 g/L, the mean clearance was 4.1±0.8 mL/h and the mean half life 39±7.8 days. Mean recovery, the increase in serum IgG concentration as a percentage of the expected concentration after an Intragam® P infusion, was 44.8±2.0%. (See CLINICAL TRIALS).

CLINICAL TRIALS
Primary Immune Deficiency

The efficacy of Intragam® P was assessed in 35 patients (age 6-76 years, 21 male) with primary immune deficiency disorders, following the administration of monthly intravenous infusions of Intragam® P for six months. The dose of Intragam® P was individualised in the range 0.2 to 0.67 g/kg. The mean number of days of hospitalisation over the 6 month period was 2.8±6.9 and the mean number of days absent from work or school due to illness, 5.3±6.4. These figures were similar to historical data relating to other intravenous immunoglobulins.

Idiopathic Thrombocytopenic Purpura (ITP)

The efficacy of Intragam® P was assessed in 17 patients (age 21-72 years, 5 male) with ITP (6 acute, 11 chronic), involving 1,264 courses of treatment. The dose of Intragam® P was individualised up to a maximum total cumulative dose of 2 g/kg bodyweight. Following administration of Intragam® P, a total of 13 patients (76.5%) achieved platelet count responses which were good (76.5%±15.0×10⁹/L) or excellent (>150×10⁹/L). Platelet counts were maintained at >50×10⁹/L for up to 35 days with a median of 17.24 days (95% CI 10.35, 24.12). These figures were similar to historical data relating to other intravenous immunoglobulins.

Adverse events encountered during both clinical trials are outlined in ADVERSE REACTIONS.

Guillain-Barré Syndrome (GBS)

There are several randomised controlled clinical trials demonstrating the efficacy and safety of the use of human intravenous immunoglobulins (IVIgs) in the treatment of patients with GBS. A large multicentre study with 379 patients (age > 16 years and with neuropsychiatric symptoms within the past 14 days) was randomised into 3 treatment arms (n=130 for IVIG, n=121 for plasma exchange (PE) and n=128 for PE followed by IVIG). The IVIG dose used was 0.4 g/kg/day for 5 days. Overall, IVIG and PE therapies were equally efficacious in the management of GBS. IVIG therapy was effective in improving both the primary and secondary GBS efficacy parameters such as disability grade, vital capacity, distally evoked compound muscle action potential, time to unaided walking, average rate of recovery etc.

The adverse reactions reported in the literature for IVIG when used in GBS treatment were consistent with those reported for other indications (see ADVERSE REACTIONS).

Intragam® P has similar characteristics to other IVIGs and has been used in the management of GBS.

INDICATIONS

Intragam® P is indicated for replacement IgG therapy in:

- primary immunodeficiency;
- myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections;
- congenital or acquired immune deficiency syndrome with recurrent infections.

Intragam® P is indicated for immunomodulatory therapy in:

- Idiopathic Thrombocytopenic Purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count;
- iatrogenic bone marrow transplantation;
- Kawasaki disease;
- Guillain-Barré Syndrome (GBS).

Comprehensive evidence-based guidelines describing appropriate clinical use of intravenous immunoglobulin in ITP have been published and should be followed wherever possible to avoid the inappropriate utilisation of this blood product 1,2.

CONTRAINDICATIONS

Intragam® P is contraindicated in patients who have had a true anaphylactic reaction to a human immunoglobulin preparation.

PRECAUTIONS

Intragam® P should only be administered intravenously. Other routes of administration have not been evaluated. It is possible that Intragam® P may, on rare occasions, cause a precipitous fall in blood pressure and a clinical picture of anaphylaxis. Therefore, adrenaline and oxygen should be available for the treatment of such an acute reaction.

Intragam® P contains trace amounts of IgA which may provoke anaphylaxis in patients with IgA antibodies, such as those with IgA deficiency.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IVIG treatment. 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, predominantly from the granulocytic series, and elevated protein levels. 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. Discontinuation of IVIG treatment has resulted in remission of AMS within several days without sequelae.

There have been occasional reports of renal dysfunction and acute renal failure in patients receiving IVIG products. Patients at increased risk are those with pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis and paraproteinemia, and those taking concomitant nephrotoxic drugs. The majority of such incidents have been associated with sucrose-containing products. Whilst there is no sucrose in Intragam® P the following precautions should be followed: Patients should be adequately hydrated prior to the initiation of the IVIG infusion and the recommended dose should not be exceeded. Renal function should be monitored in patients at increased risk of developing acute renal failure. If renal function deteriorates, discontinuation of IVIG should be considered.

Positive direct antiglobulin tests and red cell haemolysis have been reported following high dose infusion of intravenous immunoglobulin due to the presence of anti-A, anti-B, and occasionally anti-D or other erythrocyte antibodies in the product. Such red cell sensitisation may cause crossmatching difficulties and transient haemolytic anaemia.

Patients of blood group A or AB receiving high dose IVIG (>0.4 g/kg every 4 weeks) especially those with reduced bone marrow reserve or post haemopoietic stem cell transplantation appear to be more susceptible. Patients receiving high dose IVIG (>0.4 g/kg every 4 weeks) should have a pre-infusion ABO blood group determined and have their haemoglobin monitored in the days following therapy for evidence of clinically significant haemolysis.

Thrombotic events have been reported in association with IVIG therapy. Risk factors include advanced age, immobility, impaired cardiac output, and conditions associated with increased plasma viscosity, such as hypertrophic cardiomyopathy and monoclonal gammopathies.

In patients with a normal acid-base compensatory mechanism, the acid load delivered by the largest dose of the preparation would be neutralised by the buffering capacity of whole blood alone, even if the dose were to be infused instantaneously. In patients with limited or compromised acid-base compensatory mechanisms including neonates, consideration should be given to the effect of the additional acid load that the preparation might present.

Prolonged administration (over 6 hours) using large doses (greater than 0.4 g/kg) may result in thrombophlebitis at the infusion site.

Patients who receive IVIG:

- for the first time,
- when there has been a long interval since the previous infusion or,
- in rare cases, when the human normal immunoglobulin product is switched,

may experience a higher frequency of adverse events, including those of a minor nature.

Reactions to IVIG tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient’s vital signs and general status are monitored regularly throughout the infusion.

Pathogen Safety

This product is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theorhetically Creutzfeldt-Jacob Disease (CJD) agents, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, virus removal and inactivation procedures are included in the manufacturing process. The current procedures applied in the manufacture of this product are effective against enveloped viruses such as HIV (human immunodeficiency virus), hepatitis B and C viruses, and the non-enveloped virus, hepatitis A. These procedures may be of limited value against the non-enveloped virus, parvovirus B19. However, the product contains specific antibodies directed against parvovirus B19.
itching, tissue swelling, change in blood pressure, nausea or skin rash, cutaneous vasculitis, pompholyx on hands/palms. The types of reactions that may occur include: malaise, abdominal reserve or post haemopoietic stem cell transplantation. Group A or AB particularly in recipients with reduced bone marrow reserve or post haemopoietic stem cell transplantation.

ADVERSE EFFECTS

Patients naïve to immunoglobulin may experience a higher frequency of adverse events, including those of a minor nature. Reactions to intravenous immunoglobulin tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. It is recommended that the patient’s vital signs and general status are monitored regularly throughout the infusion.

Reactions Associated with Intragam® P in Clinical Trials

Primary Immune Deficiency

The following adverse reactions occurred in 35 patients receiving Intragam® P during the clinical trial (expressed as the number of patients experiencing the adverse reaction): headache (8), migrane (2), anaphylaxis (2), nausea (2), vomiting (2), allergic reaction (2), urticaria (2), angioedema (2), bronchospasm or hypotension occur very rarely. Should an anaphylactic reaction to Intragam® P develop, the infusion should be stopped and treatment instituted with adrenaline, oxygen, antihistamine and steroids.

Haemolytic anaemia and neutropenia have been reported in rare instances in association with IVIG treatment. Mild and moderate elevations of serum transaminases (AST, ALT), gamma GT have been observed in a small number of patients given IVIG. Such changes were transient and not associated with the transmission of hepatitis. Elevated liver function tests have been reported in some untreated patients with Guillain-Barré Syndrome (GBS).

An aneptic meningitis syndrome (AMS) and thromboplatinthesis have occurred in patients receiving IVIG (see PRECAUTIONS). Thrombotic events have been reported in association with IVIG therapy. Rarely, renal dysfunction and acute renal failure have been reported (see PRECAUTIONS).

DOSEAGE AND ADMINISTRATION

Dosage

Intragam® P may be infused undiluted. Intragam® P may also be diluted with up to 2 parts of 0.9% saline or 5% glucose. The infusion should be commenced at the rate of 1 mL per minute. After 15 minutes the rate may be gradually increased to a maximum of 3 to 4 mL per minute over a further 15 minutes. Consideration should be given to reducing the rate of infusion in elderly patients and in patients with pre-existing renal disease. A rate of infusion which is too rapid may cause flushing and changes in heart rate and blood pressure.

Replacement Therapy

The optimal dose and frequency of administration of Intragam® P must be determined for each patient. Frequent from recurrent bacterial infections is usually achieved with a serum IgG level above 5 g per litre. Most patients receive a dose of 0.2 to 0.6 g/kg per kilogram body weight per month, either as a single dose or as two equal doses at fortnightly intervals. Following initial diagnosis, higher doses (0.4 to 0.6 g/kg per kilogram body weight per month) may be required for several months to provide rapid protection against recurrent infections. Adjustment of both dose and infusion interval is empirical and should be based on the patient’s clinical state and the pre-infusion IgG level.

Immunomodulatory Therapy

Idiopathic Thrombocytopenic Purpura (ITP)

The following adverse reactions occurred in 17 patients receiving Intragam® P during the clinical trial (expressed as the number of patients experiencing the adverse reaction): headache (10), positive direct Coombs test (5), haemolytic anaemia (4), nausea (3), rigors (3), fever (2), myalgia (1), somnolence (1), abdominal pain (1), vomiting (1), hypertension (1), flushing (1), haemolytic anaemia (1), leukopenia (1), reticulocytosis (1), lymphopenia (1), allergic reaction (1), hot flushes (1) and injection site inflammation (1). The dose of Intragam® P ranged from 0.66 to 2 g per kg body weight received via infusion once daily over 1–3 consecutive days.

Reactions Associated with Intragam® P Use Points

Haemolytic anaemia associated with the presence of anti-A antibodies has been reported following high dose therapy (>0.4 g/kg per week) with Intragam® P in patients of blood group A or AB particularly in recipients with reduced bone marrow reserve or post haemopoietic stem cell transplantation.

Reactions Associated with Intravenous Immunoglobulins

The types of reactions that may occur include: malaise, abdominal pain, Headache, chest-tightness, facial flushing or pallor, oedema, hot sensations, dyspnoea or respiratory difficulty, non-urticarial skin rash, cutaneous vasculitis, plicophyly on hands/palms, itching, tissue swelling, change in blood pressure, nausea or vomiting. Should any of these reactions develop during infusion of Intragam® P the infusion should be temporarily stopped until the patient improves clinically (5 to 10 minutes) and then cautiously recommenced at a slower rate.

Some patients may develop delayed adverse reactions to intravenous immunoglobulin (IVIG) such as: nausea, vomiting, chest pain, rigor, dizziness, aching legs or arthralgia. These adverse reactions occur after the infusion has stopped but usually within 24 hours.

True hypersensitivity reactions to IVIG such as urticaria, angioedema, bronchospasm or hypotension occur very rarely. Should an anaphylactic reaction to Intragam® P develop, the infusion should be stopped and treatment instituted with adrenaline, oxygen, antihistamine and steroids.

Use during Pregnancy and Lactation

Passively acquired antibody can interfere with the response to live, attenuated vaccines. Therefore, administration of such vaccines, e.g. poliomyelitis or measles, should be deferred until approximately three months after passive immunisation. By the same token, immunoglobulins should not be administered for at least two weeks after a vaccine has been given.

Interactions with other Medicines

The interaction of Intragam® P with other drugs has not been established in appropriate studies.

Passively acquired antibody can interfere with the response to live, attenuated vaccines. Therefore, administration of such vaccines, e.g. poliomyelitis or measles, should be deferred until approximately three months after passive immunisation. By the same token, immunoglobulins should not be administered for at least two weeks after a vaccine has been given.

Intragam® P may interfere with some blood glucose meters, resulting in the overestimation of blood glucose results. If this glucose measurement is used to guide treatment, hypo/ hyperglycaemia may occur. Only certain glucose tests using glucose dehydrogenase have been implicated, so when monitoring glucose levels in patients receiving Intragam® P, information from the manufacturer of the glucose meter and/or test strip should be reviewed to ensure that mannose does not interfere with the blood glucose reading. Infusion of Intragam® P may also result in transient glycosuria.

Adverse Effects

The maltose present in Intragam® P may interfere with some blood glucose meters, resulting in the overestimation of blood glucose results. If this glucose measurement is used to guide treatment, hypo/ hyperglycaemia may occur. Only certain glucose tests using glucose dehydrogenase have been implicated, so when monitoring glucose levels in patients receiving Intragam® P, information from the manufacturer of the glucose meter and/or test strip should be reviewed to ensure that mannose does not interfere with the blood glucose reading. Infusion of Intragam® P may also result in transient glycosuria.

OVERDOSAGE

Overdosage may lead to fluid overload and hyperosmolarity, particularly in the elderly and in patients with renal impairment.

PRESENTATION AND STORAGE CONDITIONS

This product is available in 10, 50, and 200 mL vials containing 0.6, 1.2 and 2 g of IgG and 1.5, and 20 g of maltose respectively. Store at 2°C to 8°C. Refrigerate. Do not freeze. Once removed from refrigeration, store below 25°C and use within 3 months. Protect from light. Do not use after the expiry date.

REFERENCES


NAME AND ADDRESS OF SPONSOR

CSL Limited ABN 99 051 588 348
Bioplasma Division
189 - 209 Camp Road
Broadbeach VIC 3047
Australia

Distributed by Australian Red Cross Blood Service

POISON SCHEDULE OF THE MEDICINE

Date of therapeutic goods administration approval: March 2007

Date of most recent amendment: 07 December 2007

Registered Trademark of CSL Limited.

CSL Limited, Bioplasma Division, 189-209 Camp Road Broadbeach, Victoria Australia 3047
ABN 99 051 588 348

www.cslbioplasma.com.au

For Medical/Technical Inquiries: 1800 567 140 For Customer Service Inquiries: 1800 683 092
Email: medicalbffs@bioplasma.com.au Email: bioplasma@customer.services.com.au

Version 1909 007-0000100 CSL Bioplasma 584.