

# INTRAGAM<sup>®</sup> P

Human Normal Immunoglobulin, solution for intravenous injection

## Product Information

### Australia

#### NAME OF THE MEDICINE

Human Normal Immunoglobulin solution for intravenous injection.

#### DESCRIPTION

Intragam<sup>®</sup> 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. Isotonicity 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<sup>®</sup> P is, on the average, 61% IgG<sub>1</sub>, 36% IgG<sub>2</sub>, 3% IgG<sub>3</sub> and 1% IgG<sub>4</sub>. Intragam<sup>®</sup> P contains only trace amounts of IgA (nominally < 0.025mg/mL). Intragam<sup>®</sup> P is intended for intravenous administration.

Intragam<sup>®</sup> P is made by chromatographic fractionation of large pools 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 60°C for 10 hours) and incubation 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<sup>®</sup> P for six months. The dose of Intragam<sup>®</sup> 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±7.8 days. Mean recovery, the increase in serum IgG concentration as a percentage of the expected concentration after an Intragam<sup>®</sup> P infusion, was 44.0±2.0%. (See **CLINICAL TRIALS**).

#### CLINICAL TRIALS

##### Primary Immune Deficiency

The efficacy of Intragam<sup>®</sup> 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<sup>®</sup> P for six months. The dose of Intragam<sup>®</sup> 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±9.0 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<sup>®</sup> P was assessed in 17 patients (age 21-72 years; 5 male) with ITP (6 acute, 11 chronic), following intravenous infusion of Intragam<sup>®</sup> P once daily for 1-3 consecutive days. The dose of Intragam<sup>®</sup> P was individualised up to a maximum total cumulative dose of 2 g/kg bodyweight. Following administration of Intragam<sup>®</sup> P, a total of 13 patients (76.5%) achieved platelet count responses which were good (50x10<sup>9</sup>/L-150x10<sup>9</sup>/L) or excellent (>150 x10<sup>9</sup>/L). Platelet counts were maintained at ≥50 x10<sup>9</sup>/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 neuropathic 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<sup>®</sup> P has similar characteristics to other IVIGs and has been used in the management of GBS.

#### INDICATIONS

Intragam<sup>®</sup> 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<sup>®</sup> 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;
- allogeneic 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 <sup>1,2</sup>.

#### CONTRAINDICATIONS

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

#### PRECAUTIONS

Intragam<sup>®</sup> P should only be administered intravenously. Other routes of administration have not been evaluated. It is possible that Intragam<sup>®</sup> 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<sup>®</sup> 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 paraproteinaemia, 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<sup>®</sup> 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 hypertriglyceridaemia 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 theoretically 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 hepatitis 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.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

#### Mutagenicity, Carcinogenicity and Impairment of Fertility

No mutagenicity, carcinogenicity or reproductive toxicity studies have been conducted with Intragam® P. There have been no reports of such effects associated with the use of CSL's plasma derived products.

#### Use during Pregnancy and Lactation

The safety of this medicinal product for use in human pregnancy and lactation has not been established in controlled clinical trials. Intragam® P should therefore only be given with caution to pregnant women and breast feeding mothers. Immunoglobulins are excreted in breast milk. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

#### 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.

#### Interference with Glucose Estimation

The maltose present in Intragam® P may interfere with some blood glucose measurements, resulting in the overestimation of blood glucose results. If this glucose measurement is used to guide treatment, hypoglycaemia 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 strips, should be reviewed to ensure that maltose does not interfere with the blood glucose reading. Infusion of Intragam® P may also result in transient glucosuria.

#### ADVERSE EFFECTS

Patients naive 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), migraine (2), anaemia (2), nausea (2), vertigo (1), neutropenia (1), thrombocytopenia (1) and fatigue (1). The dose of Intragam® P ranged from 0.2 to 0.67 g per kg bodyweight per month.

##### 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), haemolysis (4), nausea (3), rigors (3), fever (2), myalgia (1), somnolence (1), abdominal pain (1), vomiting (1), hypertension (1), flushing (1), haemolytic anaemia (1), leucopenia (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 bodyweight received via infusion once daily over 1-3 consecutive days.

#### Reactions Associated with Intragam® P Use Post-Marketing

Haemolytic anaemia associated with the presence of anti-A antibodies has been reported following high dose therapy (>0.4 g/kg every 4 weeks) 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, erythema, hot sensations, dyspnoea or respiratory difficulty, non-urticarial skin rash, cutaneous vasculitis, pompholyx 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, rigors, 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.

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 aseptic meningitis syndrome (AMS) and thrombophlebitis 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**).

#### DOSAGE AND ADMINISTRATION

##### Dosage

Intragam® P may be infused undiluted. Intragam® P may also be infused 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. Freedom 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 IgG 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 IgG 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 optimal dose and frequency of administration of Intragam® P must be determined for each patient. Patients may receive a dose of up to a maximum total cumulative dose of 2 g IgG per kilogram body weight, over two to five days. Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state.

###### Kawasaki disease

The optimal dose and frequency of administration of Intragam® P must be determined for each patient. Patients should receive 1.6-2.0 g IgG per kilogram body weight, administered in divided doses over two to five days or 2 g IgG per kilogram body weight as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

###### Allogeneic bone marrow transplantation

Treatment with Intragam® P may be used as part of the conditioning regime and after the transplant. The optimal dose and frequency of administration of Intragam® P should be individualised. A starting dose of 0.5 g IgG per kilogram body weight per week is recommended.

###### Guillain-Barré Syndrome (GBS)

Intragam® P should be administered at a dose of 0.4g IgG per kilogram body weight per day for 5 days.

#### Administration

If the product appears to be turbid by transmitted light or contains any sediment, it must not be used, and the bottle should be returned unopened to the Blood Transfusion Service.

**Intragam® P contains no antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Any unused portion should be discarded. Use in one patient on one occasion only. Do not use if the solution has been frozen.**

Intragam® P should be administered separately from other intravenous fluids or medications the patient might be receiving.

Intragam® P may be administered through any standard I.V. infusion giving set. The following procedure is recommended:

1. Allow the preparation to reach room temperature before use.
2. Remove the plastic cover from the seal.
3. Apply a suitable antiseptic to the exposed part of the rubber stopper and allow to dry.
4. Stand the bottle upright and insert the air vent needle vertically in one of the indentations of the stopper. It is preferable to use a long airway needle fitted with a filter. If not available, a short needle attached to a non-wettable filter may be used.
5. Clamp the tubing of the giving set and insert the needle at the upper end of the giving set vertically through another indentation of the stopper. Should the stopper become dislodged, do not use this bottle and discard the solution appropriately.
6. Invert the bottle and attach the hanger to a support approximately one metre above the patient.
7. Allow the tubing to fill by adjusting the clamp. Attach the giving set to the venous access device (canula) and adjust the rate of flow.
8. When the bottle is empty, clamp the tubing and transfer the needle at the upper end of the giving set to a further bottle of Intragam® P.
9. Should leakage become evident during administration, cease the infusion and discard the solution appropriately. Recommence the infusion with a new bottle and giving set.

#### OVERDOSAGE

Overdosage may lead to fluid overload and hyperviscosity, 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, 3 and 12 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

1. George, JN *et al*: Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology. Blood 88, 3-40, 1996.
2. The American Society of Hematology ITP Guideline Panel: Diagnosis and Treatment of Idiopathic Thrombocytopenic Purpura: Recommendations of The American Society of Hematology. Ann Intern Med 126, 319-326, 1997.

#### NAME AND ADDRESS OF SPONSOR

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#### POISON SCHEDULE OF THE MEDICINE

S4

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