AUSTRALIAN PRODUCT INFORMATION

Intragam® P

(Human normal immunoglobulin)

1 NAME OF THE MEDICINE

Human Normal Immunoglobulin

2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION and PHARMACEUTICAL FORM

Intragam® P is a sterile, preservative free solution for intravenous infusion 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® P is, on the average, 61% IgG_1, 36% IgG_2, 3% IgG_3 and 1% IgG_4. Intragam® P contains only trace amounts of IgA (nominally <0.025 mg/mL).

Intragam® P is manufactured from human plasma collected by the Australian Red Cross Blood Service.

Excipient of known effect: maltose.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Intragam® P is indicated for replacement IgG therapy in:

- Primary Immunodeficiency Diseases (PID)
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

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
- 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].

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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/litre. Most patients receive a dose of 0.2–0.6 g IgG/kilogram body weight/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/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/kilogram body weight, administered in divided doses over two to five days or 2 g IgG/kilogram body weight as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Guillain-Barré Syndrome (GBS)

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

Administration

NOTE: Intragam® P contains no antimicrobial preservative. It must therefore, be used immediately after opening the bottle. Use in one patient on one occasion only. Any unused portion should be discarded appropriately. Do not use if the solution has been frozen. If Intragam® P appears to be turbid or to contain any sediment, it must not be used. The unopened bottle should be returned to the Australian Red Cross Blood Service.

Intragam® P is intended for intravenous administration.

The infusion should be commenced at the rate of 1 mL/minute. After 15 minutes the rate may be gradually increased to a maximum of 3–4 mL/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.

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

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.

Intragam® P may be administered through any standard IV 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 (cannula) 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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Aseptic meningitis syndrome

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.

Acute renal failure

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® 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.

Haemolytic anaemia

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 at increased risk include those with blood group A, B or AB, or who have underlying associated inflammatory conditions. Also at risk are patients receiving high dose IVIG (>0.4 g/kg every 4 weeks) especially those with reduced bone marrow reserve or post haemopoietic stem cell transplantation.

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

Thrombotic events have been reported in association with IVIG therapy. Risk factors include advanced age, immobility, oestrogen use, in-dwelling vascular catheters, acquired or inherited hypercoagulable states, a history of venous or arterial thrombosis, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), and conditions associated with increased plasma viscosity, such as fasting chylomicronaemia and/or high triglyceride levels, cryoglobulins and monoclonal gammopathies.

Patients at risk for thrombotic events should receive product at the minimum infusion rate and dose practicable, and should be monitored for thrombotic complications. Consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity.

Acid load

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.

Thrombophlebitis

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

General

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-Jakob 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.

Use in the elderly

Clinical studies of Intragam® P did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently to younger subjects.

Paediatric use

The use of Intragam® P in the paediatric population has not been established in clinical studies.

Effects on laboratory tests

Interference with glucose estimations

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The interaction of Intragam® P with other medicines 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been conducted with Intragam® P.

Use in pregnancy

The safety of Intragam® P for use in human pregnancy has not been established in controlled clinical trials. Intragam® P should therefore only be given with caution to pregnant women. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus are to be expected.

Use in lactation

The safety of Intragam® P for use in lactation has not been established in controlled clinical trials. Intragam® P should therefore only be given with caution to breast feeding mothers. Immunoglobulins are excreted in breast milk. Clinical experience with immunoglobulins suggests that no harmful effects on the neonate are to be expected.

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)

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 Immunodeficiency Diseases (PID)

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/kg body weight/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/kg body weight 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 and/or anti-B antibodies has been reported following high dose therapy (>0.4 g/kg every 4 weeks) with Intragam® P in patients of blood group A, B or AB particularly in recipients with reduced bone marrow reserve or post haemopoietic stem cell transplantation.

In addition to the reactions observed in clinical trials, the following were observed post-marketing:

Immune system disorders: anaphylactic reactions/hypersensitivity
Nervous system disorders: Aseptic Meningitis Syndrome (AMS), paraesthesia, tremor
Vascular disorders: thromboembolism
Skin and subcutaneous tissue disorders: exfoliative dermatitis
Musculoskeletal and connective tissue disorders: arthralgia
General disorders and administration site conditions: infusion site reactions, pain.

Reliable estimates of the frequency of these reactions or establishment of a causal relationship to product exposure are not possible because the reporting is voluntary and from a population of uncertain size.

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 section 4.4 Special warnings and precautions for use).

Thrombotic events have been reported in association with IVIG therapy. Rarely, renal dysfunction and acute renal failure have been reported (see section 4.4 Special warnings and precautions for use).

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 any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosage may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with 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

Mechanism of action

Intragam® P is made by chromatographic fractionation of large pools of human plasma. The protein has not been chemically or enzymatically modified. The manufacturing process contains dedicated steps to reduce the possibility of virus transmission including pasteurisation (60°C for 10 hours) and incubation at low pH.

Clinical trials

Primary Immunodeficiency Diseases (PID)

The efficacy of Intragam® P was assessed in 35 patients (age 6–76 years; 21 male) with primary immunodeficiency diseases, following the administration of monthly intravenous infusions of Intragam® P for six months. The dose of Intragam® P was individualised in the range 0.2–0.67 g/kg. The mean number of days of hospitalisation over the six month period was 2.8±9.0 and the mean number of days absent from work or school due to illness was 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), following intravenous infusion of Intragam® P once daily for 1–3 consecutive days. The dose of Intragam® P was individualised up to a maximum total cumulative dose of 2 g/kg body weight. Following administration of Intragam® P, a total of 13 patients (76.5%) achieved platelet count responses which were good (50×10^9/L–150×10^9/L) or excellent (>150×10^9/L). Platelet counts were maintained at ≥50×10^9/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 section 4.8 Adverse effects (Undesirable effects).

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 and average rate of recovery.

The adverse reactions reported in the literature for IVIG when used in GBS treatment were consistent with those reported for other indications (see section 4.8 Adverse effects (Undesirable effects)).

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

5.2 PHARMACOKINETIC PROPERTIES

The steady-state kinetic parameters for serum IgG were determined in 11 patients (9 male, age 28–76 years) with primary immunodeficiency diseases, following the administration of monthly intravenous infusions of Intragam® P for six months. The dose of Intragam® P was individualised in the range 0.35–0.53 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® P infusion, was 44.0±2.0% (see section 5.1 Pharmacodynamic properties- Clinical trials).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with Intragam® P.

Carcinogenicity

No carcinogenicity studies have been conducted with Intragam® P.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Refer to Section 4.2 Dose and method of administration.

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 (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.

6.5 NATURE AND CONTENTS OF CONTAINER

This product is available in 10, 50, 200 and 500 mL vials containing 0.6, 3, 12 and 30 g of IgG and 1, 5, 20 and 50 g of maltose respectively.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

No data available

CAS number

9007-83-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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Australian Red Cross Blood Service

9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

19 November 2018

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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.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	PI reformatted in line with TGA requirement
4.8	Addition of exfoliative dermatitis as a post-marketing adverse reaction