NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Intragam® P 6% solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Normal Immunoglobulin

Intragam® P is a sterile, preservative-free solution containing 6 g of human protein in each 100 mL. 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 donated by New Zealand's voluntary and non-remunerated donors.

Intragam® P contains 10 g of maltose in each 100 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intragam® P is a solution for intravenous infusion.

Intragam® P is isotonic, with an approximate osmolality of >240 mOsm/kg.

The solution has a pH of 4.25.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults and children:

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

Immunomodulatory therapy in adults and children:

- Idiopathic Thrombocytopenic Purpura (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barré Syndrome (GBS).
- Kawasaki disease.

Comprehensive evidence-based guidelines describing appropriate clinical use of intravenous immunoglobulin (IVIg) 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

Dose

Replacement therapy

Replacement therapy should be commenced and monitored under the supervision of a healthcare professional experienced in the treatment of immunodeficiency.

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/kg body weight (bw)/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/kg bw/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/kg bw, over 2 to 5 days Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state.

Guillain-Barré Syndrome (GBS)

Intragam® P should be administered at a dose of 0.4 g IgG/kg bw/day, over 5 days.

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/kg bw, administered in divided doses over 2 to 5 days or 2 g IgG/kg bw as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Paediatric population

The dose in children is not different from that of adults as the dose for each indication is given by body weight and adjusted based on the pre-infusion IgG level and/or the clinical outcome.

Method of administration

For intravenous use.

The infusion should be commenced at the rate of 1 mL/minute (60 mL/hour). After 15 minutes the rate may be gradually increased to a maximum of 3–4 mL/minute (180–240 mL/hour) over a further 15 minutes. Consideration should be given to reducing the rate of infusion in patients naive to Intragam® P, patients switching from an alternative IVIg, patients who have not received IVIg for a long time, paediatric and elderly patients and in patients with pre-existing renal disease (see section 4.4).

A rate of infusion which is too rapid may cause flushing and changes in heart rate and blood pressure.

Intragam® P may be infused undiluted. It may also be infused diluted with up to 2 parts of 0.9% saline or 5% glucose.

For further instructions, see sections 4.4 and 6.6.

4.3 Contraindications

Intragam® P is contraindicated in patients:

- who have had a true anaphylactic reaction to a human immunoglobulin preparation
- who are IgA-deficient with antibodies to IgA and a history of hypersensitivity
- with a history of hypersensitivity to the excipient maltose.

4.4 Special warnings and precautions for use

Intragam® P should only be administered intravenously. Other routes of administration have not been evaluated.

General

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. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- in patients with hypogammaglobulinaemia or agammaglobulinaemia with or without IgA deficiency
- in patients who receive human immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Hypersensitivity

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

Rarely, human normal immunoglobulin can induce a precipitous fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin. In case of anaphylactic reaction, the infusion should be stopped immediately. Adrenaline (epinephrine) and oxygen should be available for the treatment of such an acute reaction.

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 monoclonal gammopathy, and those taking concomitant nephrotoxic drugs. While these reports of renal dysfunction and acute renal failure have been associated with many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. Intragam® P contains maltose but it does not contain sucrose. 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.

In patients at risk of acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose possible, based on clinical judgement.

Thromboembolic Events

Thromboembolic events have been reported in association with IVIg therapy. Risk factors include advanced age, immobility, estrogen 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 cryoglobulins, fasting chylomicronaemia and/or hypertriglyceridaemia and monoclonal gammopathies.

Patients at risk for thromboembolic events should receive IVIg products at the minimum infusion rate and dose possible based on clinical judgement, and should be monitored for thromboembolic complications. Consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity.

Aseptic Meningitis Syndrome

Aseptic Meningitis Syndrome (AMS) has been reported to occur 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.

Haemolytic Anaemia

Positive direct antiglobulin tests and red blood cell haemolysis have been reported following high dose infusion of IVIg due to the presence of blood group antibodies (e.g. anti-A, anti-B, and

occasionally anti-D or other erythrocyte antibodies) in the product. Such red blood cell sensitisation may cause crossmatching difficulties and transient haemolytic anaemia.

The following risk factors are associated with the development of haemolysis: high doses, non-O blood group, and underlying inflammatory state.

Patients receiving 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.

If signs and/or symptoms of haemolysis develop during or after an IVIg infusion, discontinuation of the IVIg treatment should be considered by the treating physician.

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 (>0.4 g/kg) may result in thrombophlebitis at the infusion site.

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.

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 with the use of CSL Behring's plasma derived products.

Recording during treatment

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

4.5 Interaction with other medicines and other forms of interaction

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

Live attenuated virus vaccines

Passively acquired antibody can interfere with the response to live, attenuated vaccines. Therefore, administration of such vaccines, e.g. poliomyelitis, mumps, rubella, measles and varicella/chickenpox vaccines, should be deferred until approximately three months after passive immunisation. Immunoglobulins should not be administered for at least two weeks after a vaccine has been given. In the case of measles vaccinations, the decrease in efficacy may persist for up to a year. Patients given measles vaccine should therefore have their antibody status checked.

Interference with serological testing

After immunoglobulin infusion the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens (e.g. anti-A, Anti-B, anti-D) may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs' test).

Interference with glucose measurement

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.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

The safety of Intragam® P 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.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with Intragam® P. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Patients naive to immunoglobulin 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.

Adverse reactions from clinical trials

Primary Immunodeficiency Diseases (PID)

The following adverse reactions occurred in 35 PID 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/month.

Idiopathic Thrombocytopenic Purpura (ITP)

The following adverse reactions occurred in 17 ITP 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 received via infusion once daily over 1–3 consecutive days.

Adverse reactions from spontaneous reporting

Haemolytic anaemia associated with the presence of anti-A and/or anti-B antibodies has been reported following high dose therapy with Intragam® P in patients of non-O blood group (blood group A, B or AB).

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

Immune system disorders: Anaphylactic reaction/Hypersensitivity
Nervous system disorders: Meningitis aseptic, Paraesthesia, Tremor
Vascular disorders: Thromboembolism
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.

General class effects 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 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 (epinephrine), 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.

AMS and thrombophlebitis have occurred in patients receiving IVIg (see section 4.4).

Thromboembolic events have been reported in association with IVIg therapy. Rarely, renal dysfunction and acute renal failure have been reported (see section 4.4).

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Intragam® P contains functionally intact IgG present in the donor population, with a broad spectrum of antibodies against infectious agents. Adequate doses of intact IgG restore abnormally low IgG levels to the normal range in patients. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Intragam® P is prepared from pooled human plasma collected from not fewer than 1000 donors. It is made by chromatographic fractionation of the pooled human plasma. The protein is not chemically or enzymatically modified and the Fc and Fab functions are retained. It has an IgG subclass distribution closely proportional to normal human plasma. 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 efficacy and safety

PID

The efficacy of Intragam® P was assessed in 35 patients (age 6–76 years; 21 male) with PID, following the administration of monthly intravenous infusions of Intragam® P for six months. The dose of Intragam® P was individualised in the range of 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 IVIg.

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. Following administration of Intragam® P, a total of 13 patients (76.5%) achieved platelet count responses which were good (50 x 10^9/L–150 x 10^9/L) or excellent (>150 x 10^9/L). Platelet counts were maintained at

≥50 x 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 IVIg.

Paediatric population

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

Elderly

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

5.2 Pharmacokinetic properties

Absorption

Intragam® P is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution

Intragam® P is distributed relatively rapidly between plasma and extravascular fluid. Equilibrium between the intravascular and extravascular compartments is reached after approximately 3 to 5 days.

Elimination

The half-life of Intragam® P may vary from patient to patient. IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

The steady-state kinetic parameters for serum IgG were determined in 11 patients (9 male, age 28–76 years) with PID, 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%.

5.3 Preclinical safety data

Immunoglobulins are natural components of the human body. Data from animal testing of acute and chronic toxicity and embryofoetal toxicity of immunoglobulins are inconclusive on account of interactions between immunoglobulins from heterogeneous species and the induction of antibodies to heterologous proteins.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose
Water for injections

6.2 Incompatibilities

This medicine must not be mixed with other medicines, diluents, or solvents except those mentioned in section 6.6, and should be administered by a separate infusion line.

6.3 Shelf life

2 years at 2°C to 8°C

Shelf life after first opening:

Intragam® P contains no antimicrobial preservative. It must, therefore, be used immediately after opening the bottle.

Temporary storage:

Shelf life of 3 months when not refrigerated (below 25°C).

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.

Do not use if the solution has been frozen.

Protect from light.

For storage conditions after first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

Solution in a single vial (type I glass), with a rubber closure, an aluminium seal, a flip-top cap (plastic).

Pack sizes

One bottle of 10 mL solution containing 0.6 g human normal immunoglobulin.
One bottle of 50 mL solution containing 3 g human normal immunoglobulin.
One bottle of 200 mL solution containing 12 g human normal immunoglobulin.
One bottle of 500 mL solution containing 30 g human normal immunoglobulin.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use in one patient on one occasion only.

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 New Zealand Blood Service.

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 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.

Any unused portion should be discarded appropriately.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 March 2000

10 DATE OF REVISION OF THE TEXT

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Intragam® P is a registered trademark of CSL Limited

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
4.2	Patient groups added where reducing the rate of infusion should be considered
4.3	Contraindications added for IgA deficiency and maltose hypersensitivity
4.4	Updated for consistency with other IVIg products.
4.5	Updated for consistency with other IVIg products, particularly measles. Interference with serological testing added.
4.7	Information added about effects on ability to drive and use machines.
4.8	Updated for consistency with precaution statements
4.9	Cardiac impairment added as a risk factor in overdose.