AUSTRALIAN PRODUCT INFORMATION

Intragam® 10

(Human normal immunoglobulin)

1 NAME OF THE MEDICINE

Human Normal Immunoglobulin

2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION and PHARMACEUTICAL FORM

Intragam® 10 is a sterile, preservative free, clear or slightly opalescent and colourless or pale yellow solution for intravenous infusion. Intragam® 10 contains 10% (10 g/100 mL) of human plasma protein with a purity of at least 98% immunoglobulin G (IgG). At least 90% of the IgG consists of monomers and dimers (typically >96%). Aggregates are <3%. The distribution of the IgG subclasses closely resembles that found in normal human plasma (approximate mean ranges: 47.6–56.2% IgG_1, 41.5–49.5% IgG_2, 1.3–1.6% IgG_3, 0.9–1.3% IgG_4).

Intragam® 10 has a nominal osmolality of 350 mOsmol/kg and is approximately isotonic. The pH value of the ready-to-use solution is 4.25 (4.05–4.45). Intragam® 10 contains 2.25 g of glycine in each 100 mL as a stabiliser which is a physiological non-essential amino acid. Intragam® 10 does not contain a carbohydrate stabiliser (e.g. sucrose, maltose) and contains no preservative. Intragam® 10 contains only trace amounts of IgA, typically <0.025 mg/mL. The maximum prekallikrein activator (PKA) levels are less than 28.6 IU/mL (typically ≤1.2 IU/mL).

Intragam® 10 is manufactured from human plasma collected by Australian Red Cross Lifeblood.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Intragam® 10 is indicated for replacement IgG therapy in:

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

Intragam® 10 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)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Multifocal Motor Neuropathy (MMN)
- Myasthenia Gravis (MG) in acute exacerbation (myasthenic crisis) or prior to surgery and/or thymectomy; as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects
- Short-term therapy for severely affected nonparaneoplastic Lambert-Eaton Myasthenic Syndrome (LEMS) patients
- Treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The dosage recommendations are summarised in **Table 1***.

Table 1: Dosage recommendations

Indication	Dose	Frequency of infusion
Replacement therapy[†]		
Primary or secondary immunodeficiency	0.2–0.8 g/kg body weight (bw)	Every 3–4 weeks to achieve IgG serum level of at least 5 g/L
Immunomodulatory therapy[‡]		
Idiopathic thrombocytopenic purpura	Maximum cumulative dose of 2 g/kg bw	In divided doses over 2–5 days
Guillain-Barré Syndrome (GBS)	0.4 g/kg bw	Daily for 5 days
Kawasaki disease	1.6–2 g/kg bw or 2 g/kg bw	In divided doses over 2–5 days in association with acetylsalicylic acid As a single dose in association with acetylsalicylic acid
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Induction: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 0.4–1 g/kg bw	Every 2–6 weeks
Multifocal Motor Neuropathy (MMN)	Induction: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 0.4–2 g/kg bw	Every 2–6 weeks
Myasthenia Gravis (MG)	Prior to surgery or during myasthenic crisis Induction: 1–2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 0.4–1 g/kg bw	Every 4–6 weeks
Lambert-Eaton Myasthenic Syndrome (LEMS)	Induction: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 0.4–1 g/kg bw	Every 2–6 weeks
Stiff person syndrome	Induction: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 1–2 g/kg bw	Every 4–6 weeks

* The optimal dose and frequency of administration of Intragam® 10 must be determined for each patient.

† 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.

‡ Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state.

Administration

CAUTION: This product does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Any unused solution should be discarded appropriately. Use in one patient on one occasion only. Do not use if the solution has been frozen.

The solution must be clear or slightly opalescent. If it appears to be turbid or to contain any sediment, it must not be used and the bottle should be returned unopened to Australian Red Cross Lifeblood.

Allow the preparation to reach room temperature before use. Intragam® 10 should be administered through a standard intravenous infusion giving set. The infusion line may be primed or flushed with 0.9% saline (0.9% sodium chloride solution). Intragam® 10 should be administered separately from intravenous fluids (other than normal saline) or medications the patient might be receiving. Intragam® 10 may be infused undiluted or diluted with up to 2 parts of 0.9% saline.

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. Infusion rates higher than recommended may increase the incidence of headache. Consideration should be given to reducing the rate of infusion in patients naive to Intragam® 10, 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 Special warnings and precautions for use- General).

4.3 CONTRAINDICATIONS

Intragam® 10 is contraindicated in patients who have had a true anaphylactic reaction to human immunoglobulins (especially in patients with antibodies against IgA) or to the excipient glycine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

The recommended infusion rate of Intragam® 10 must be closely followed (see section 4.2 Dose and method of administration). Certain reactions (including severe reactions) to IVIg tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. In case of adverse reaction, the rate of administration should be reduced or the infusion stopped to alleviate symptoms. Once a reaction has resolved, based on clinical judgement, the infusion may cautiously be recommenced at a slower rate.

Certain adverse reactions may occur more frequently:

- with a higher infusion rate
- in patients with hypo- or agammaglobulinemia with or without IgA deficiency
- in patients who receive human normal 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.

Potential complications can often be avoided by ensuring that:

- patients are not sensitive to human normal immunoglobulin by first infusing the product slowly (1 mL/min)

- patients are carefully monitored for any symptoms throughout the infusion period
- the infusion rate is reduced in patients who are naive to Intragam® 10 or who are at increased risk of adverse events.

Hypersensitivity

True hypersensitivity reactions to immunoglobulins are rare. They can occur in patients with anti-IgA antibodies, such as those with IgA deficiency. Intragam® 10 should be used with caution in patients with a known allergy to constituents of the preparation. Intragam® 10 contains traces of IgA which seldomly may provoke anaphylaxis in IgA deficient patients with anti-IgA antibodies.

Rarely, human normal immunoglobulin can induce a 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.

Acute renal failure

Cases of renal dysfunction and acute renal failure have been reported in patients receiving IVIg therapy. Risk factors may include: pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, concomitant nephrotoxic medicinal products, sepsis, paraproteinaemia, being overweight or aged over 65 years. The majority of cases of renal dysfunction and acute renal failure have been associated with the use of those IVIg products containing sucrose as a stabiliser. There is no sucrose in Intragam® 10. In case of renal impairment, IVIg discontinuation should be considered. The following precautions should be followed for all patients at risk:

- ensuring adequate hydration prior to the initiation of Intragam® 10
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant loop diuretics.

In patients at risk for renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Thrombotic events

There is clinical evidence of an association between IVIg administration and thromboembolic events which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised when prescribing and infusing IVIg for patients with pre-existing risk factors for thrombotic events such as advanced age, estrogen use, in-dwelling vascular catheters, a history of venous or arterial thrombosis, acquired or inherited hypercoagulable states, cardiovascular risk factors

(including history of atherosclerosis and/or impaired cardiac output), prolonged periods of immobilisation, severe hypovolaemia, hyperviscosity (including cryoglobulins, fasting chylomicronaemia and/or high triglyceride levels, and monoclonal gammopathies). Reports have included cases of thrombophlebitis. In case of thromboembolic adverse reaction, the benefit and risk of treatment should be assessed before IVIg therapy is continued.

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable, and these individuals should be monitored for thrombotic complications. Ensure adequate hydration prior to the initiation of Intragam® 10. 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 in association with IVIg treatment. It has been hypothesised that IVIg-associated AMS is the severe presentation of a continuum that begins with the more common adverse event of headache. The AMS 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.

Patients with a history of AMS, migraine or frequent headaches may be more susceptible to the syndrome. For these patients the following precautions should be taken:

- assessment of hydration status and ensuring adequate hydration prior to commencement of infusion of Intragam® 10
- administration of a pre-medication (e.g. paracetamol/paracetamol and codeine) if needed prior to each infusion of Intragam® 10 (e.g. if headache present)
- administration of the minimum dose at the minimum rate practicable.

Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. Patients at increased risk for haemolysis following treatment with immunoglobulin include those with blood

groups A, B, or AB, or who have underlying associated inflammatory conditions. Also at risk are patients receiving high cumulative doses of immunoglobulin over the course of several days. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis, particularly those patients at increased risk. If these occur, appropriate laboratory testing should be undertaken.

Acid load

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.

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. 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 pathogen markers. In addition, three dedicated pathogen reduction steps are included in the manufacturing process of Intragam® 10 to reduce the possibility of pathogen transmission including pasteurisation (heating at 60°C for 10 hours), nanofiltration and incubation at low pH. The current procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) viruses, and the non-enveloped viruses hepatitis A (HAV) and parvovirus B19. In addition, Intragam® 10 contains specific antibodies directed against parvovirus B19.

Despite these measures, there remains the potential that such products may transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products. Vaccination of patients in receipt of plasma-derived therapeutics should be considered where appropriate.

It is recommended that the name and batch number of the product are recorded every time the product is administered to a patient.

Use in the elderly

Clinical studies of Intragam® 10 included a total of 22 subjects aged >65 years. Based on these limited data, no overall differences in the safety profile were observed between subjects >65 years and subjects 18 to 65 years of age.

Paediatric use

The use of Intragam® 10 in the paediatric population has not been established in clinical studies.

Effects on laboratory tests

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. A, B, D) may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs' test), reticulocyte count and haptoglobin.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Live attenuated virus vaccines

Immunoglobulin infusion may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella for a period of at least six weeks and up to three months. After infusion of Intragam® 10, an interval of three months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to one year. Therefore patients receiving measles vaccine should have their antibody status checked. Additionally, immunoglobulins should not be administered for at least two weeks after these vaccines are given.

The interaction of Intragam® 10 with other medicines has not been established.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been conducted with Intragam® 10.

Use in pregnancy

No animal reproduction studies have been conducted with Intragam® 10. Intragam® 10 should be given to pregnant women only if clearly indicated.

An embryofoetal development study in which rats were infused IV with the excipient glycine 945 mg/kg/day on gestation days 6–17 showed no adverse effects.

Use in lactation

No lactation studies have been conducted with Intragam® 10. Immunoglobulins are excreted in breast milk and may contribute to the transfer of protective antibodies to the neonate.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effect on the ability to drive and use machines have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Two clinical studies with Intragam® 10 were performed, one study of 19 patients with PID and one study of 19 patients with ITP.

Causally related adverse reactions reported in these studies are summarised and categorised according to the MedDRA System organ class and frequency, calculated in percentage of patients, in **Table 2** (very common (≥10% patients), or common (≥1% and <10% patients)).

Table 2: Causally related adverse drug reactions (ADRs) observed in clinical studies with Intragam® 10

System organ class	Very common (≥10%)	Common (≥1% and <10%)
Infections and infestations	-	Meningitis aseptic*
Immune system disorders	-	Hypersensitivity*
Nervous system disorders	Headache Lethargy Migraine* Dizziness*	-
Vascular disorders	Hot flush	-
Respiratory, thoracic and mediastinal disorders	-	Dyspnoea*
Gastrointestinal disorders	Nausea Vomiting*	Abdominal pain*
Skin and subcutaneous tissue disorders	Pruritus	Rash*
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Musculoskeletal stiffness*	-
General disorders and administration site reactions	Infusion site pain* Pyrexia Pain	-

* These adverse events were only observed in the clinical study for the treatment of ITP.

Adverse events (AEs) reported by two or more patients (>10%) in the studies, ***irrespective of causal relationship to the product***, are presented in **Table 3**.

Table 3: Adverse events occurring in two or more patients (>10%) in at least one of the clinical studies with Intragam® 10, *irrespective of causality*

MedDRA System organ class **Preferred term**	**PID Patients** **N=19** **n (%)**	**ITP Patients** **N=19** **n (%)**
Infections and infestations		
Upper respiratory tract infection	8 (42.1%)	0
Lower respiratory tract infection	7 (36.8%)	0
Gastroenteritis	5 (26.3%)	0
Sinusitis	5 (26.3%)	0
Viral infection	2 (10.5%)	0
Nervous system disorders		
Headache	7 (36.8%)	15 (78.9%)
Lethargy	4 (21.1%)	2 (10.5%)
Dizziness	0	2 (10.5%)
Migraine	0	2 (10.5%)
Gastrointestinal disorders		
Nausea	3 (15.8%)	9 (47.4%)
Vomiting	0	6 (31.6%)
Diarrhoea	3 (15.8%)	1 (5.3%)
Musculoskeletal and connective tissue disorders		
Osteopenia	4 (21.1%)	0
Arthralgia	2 (10.5%)	3 (15.8%)
Myalgia	2 (10.5%)	0
Osteoporosis	2 (10.5%)	0
Musculoskeletal stiffness	0	2 (10.5%)
Pain in extremity	0	2 (10.5%)
General disorders and administration site conditions		
Fatigue	0	3 (15.8%)
Pyrexia	2 (10.5%)	1 (5.3%)
Infusion site pain	0	2 (10.5%)
Pain	2 (10.5%)	0
Respiratory, thoracic and mediastinal disorders		
Cough	4 (21.1%)	0
Injury, poisoning and procedural complications		
Animal bite	0	2 (10.5%)
Contusion	0	2 (10.5%)
Procedural pain	0	2 (10.5%)
Vascular disorders		
Hot flush	3 (15.8%)	0
Eye disorders		
Conjunctivitis	2 (10.5%)	0
Skin and subcutaneous tissue disorders		
Pruritus	2 (10.5%)	0

In a prospective observational post-authorisation safety study (PASS) to evaluate the occurrence of AMS in adults receiving ≥1 g/kg bw of Intragam® 10 for a range of indications, the primary endpoint included the occurrence of AMS, migraine and severe headache. All 39 patients enrolled were either naive to IVIg or were switched to Intragam® 10 from another IVIg product (see section 5.1 Pharmacodynamic properties). No occurrences (rate = 0%, 95% CI: 0.0 to 9.0%) of AMS or migraine were observed in this study. Severe headache occurred in 3 (7.7%) patients (2 considered serious). The following adverse events were reported in >5% of patients: headache 10 (25.6%), musculoskeletal pain (including pain in extremities) 3 (7.6%), and rash 2 (5.2%). One patient with ITP experienced cerebrovascular accident, considered serious (outcome resolved).

General class effects associated with intravenous immunoglobulins

True hypersensitivity reactions to IVIg products, such as urticaria, angioedema, bronchospasm, or a sudden drop in blood pressure, have been observed in patients. In isolated cases immunoglobulins may cause anaphylactic shock, even when the patient has shown no known hypersensitivity to previous administration (see section 4.4 Special warnings and precautions for use- Hypersensitivity). Should an anaphylactic reaction to Intragam® 10 develop, the infusion should be stopped immediately and appropriate treatment initiated.

Adverse reactions (such as chills, headache, fever, vomiting, nausea, arthralgia, changes in blood pressure or moderate lower back pain) or allergic-type reactions (such as flushing, pruritus, lethargy, restlessness, tachycardia, tingling, tissue swelling, wheezing or shortness of breath) may occur occasionally with the use of IVIg products.

Other class adverse reactions that may occur with IVIg preparations include: malaise, abdominal pain, chest-tightness, facial flushing or pallor, erythema, hot sensations, respiratory difficulty, non-urticarial skin rash, cutaneous vasculitis, or infusion/injection site reactions (such as pain, swelling, erythema, pruritus or rash at the site).

Some patients may develop delayed adverse reactions to IVIg products 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.

Cases of reversible AMS (see section 4.4 Special warnings and precautions for use- Aseptic meningitis syndrome), isolated cases of reversible haemolytic anaemia/haemolysis (see section 4.4 Special warnings and precautions for use- Haemolytic anaemia), and cases of transient cutaneous reactions, have been reported with IVIg treatment. Neutropenia has been reported in rare instances. Increase in serum creatinine level and/or acute renal failure (see section 4.4 Special warnings and precautions for use- Acute renal failure) have been observed.

Mild and moderate elevations of serum transaminases (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-Glutamyltransferase (GGT)) have been observed in a small number of patients given IVIg. Such changes were transient and not associated with the transmission of hepatitis.

Very rarely, thrombotic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses have been associated with IVIg treatment (see section 4.4 Special warnings and precautions for use- Thrombotic events).

Post-marketing experience

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

Skin and subcutaneous tissue disorders: exfoliative dermatitis.

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Intragam® 10 contains functionally intact IgG with a broad spectrum of antibodies against infectious agents.

Intragam® 10 contains the IgG antibodies present in the donor population. Adequate doses of human normal immunoglobulin restore abnormally low IgG levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Intragam® 10 is manufactured by chromatographic fractionation. It is prepared from pooled plasma collected from not fewer than 1000 donors. The IgG molecules have not been

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 three dedicated and complementary steps to reduce the possibility of pathogen transmission:

- pasteurisation (60°C for 10 hours)
- nanofiltration
- incubation at low pH.

Clinical trials

Replacement therapy

Intragam® P is CSL's 6% w/v intravenous immunoglobulin (IVIg) and parent product for Intragam® 10 which differs from Intragam® P only in formulation, concentration and additional pathogen removal step as part of the manufacturing process. The efficacy of Intragam® 10 in PID is confirmed by previous clinical trials conducted with Intragam® P, as the biological, pharmacokinetic and safety data showed no significant differences between the two products. Therefore, the following clinical trial information for Intragam® P supports the efficacy of Intragam® 10 in PID patients.

The efficacy of Intragam® P was assessed in 35 subjects (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 0.2 to 0.67 g/kg bw. 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 was 5.3±6.4. These figures were similar to historical data relating to other IVIgs.

Immunomodulatory therapy

The efficacy of Intragam® 10 in patients with ITP was established in a multi-centre open-label clinical trial, which was consistent with the results from the previous Intragam® P clinical trials. A total of 17 subjects aged 20 to 76 years with ITP and a platelet count of $<50 \times 10^9$/L were treated with 1 g/kg bw of Intragam® 10 on each of two consecutive days (a total cumulative dose of 2 g/kg bw). A rise in platelet count to at least 50×10^9/L within 7 days after the first infusion was observed in 15 of the 17 subjects studied. The median time to achieve this platelet response was 4 days after the first infusion, and 71% of the subjects reached this response within four days (i.e. two days after the second infusion). For those subjects who responded, the median duration of platelet count $\geq 50 \times 10^9$/L was 17 days (range: 7 to >85 days).

A prospective observational PASS was conducted to evaluate the occurrence of AMS in adults receiving ≥1 g/kg bw of Intragam® 10 for a range of indications. The primary endpoint included the occurrence of AMS, migraine and severe headache. A total of 39 patients were

enrolled in the study, aged 23 to 84 years, who had neurologic and haematologic conditions requiring immunoglobulin therapy for immunomodulation or immune replacement. The mean dose was 1.74 g/kg bw and the median total dose was 2.0 g/kg bw. A total of 143 infusions were given, with a median maximum infusion rate of 240 mL/hr (range: 60 to 700 mL/hr). The majority of the patients were naive to IVIg treatment (30 of 39 patients; 76.9%). Throughout the treatment period and up to 7 days after the last Intragam® 10 infusion, the most common adverse event observed was headache which occurred in 10 patients (25.6%). Severe headache was reported in 3 patients (7.7%; 95% CI: 1.62 to 20.87%). Neither AMS nor migraine (0%, 95% CI: 0.0 to 9.0%) were observed. One patient was withdrawn due to moderate rash occurring during the first infusion.

There are several other randomised controlled clinical trials available in literature demonstrating the safety and efficacy of IVIg treatment in patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multifocal Motor Neuropathy (MMN) and Myasthenia Gravis (MG). Whilst the evidence for safety and efficacy of IVIg in the management of CIDP and acute exacerbations of MG is clear, data for the treatment of chronic MG and MMN is not yet as definitive. Clinical trials for the use of IVIg for MMN showed an increase in muscle strength but no impact on the disability scale.

The safety and efficacy of IVIg in the treatment of patients with stiff person syndrome and Lambert-Eaton Myasthenic Syndrome (LEMS) has only been demonstrated in a single randomised controlled clinical trial for each condition.

The adverse reactions reported in the literature for IVIg when used in CIDP, MMN, MG, LEMS and stiff person syndrome were consistent with those reported for other IVIg indications (see section 4.8 Adverse effects (Undesirable effects)).

Intragam® 10 has shown overall similar characteristics to other IVIg products used in the management of CIDP, MMN, MG, LEMS and stiff person syndrome.

5.2 PHARMACOKINETIC PROPERTIES

Intragam® 10 is immediately and completely bioavailable in the recipient’s circulation after intravenous infusion. It is distributed relatively rapidly between plasma and extravascular fluid. After approximately 3 to 5 days, equilibrium is reached between the intra- and extravascular compartments.

The pharmacokinetic parameters for Intragam® 10 were established in a clinical study (see section 5.1 Pharmacodynamic properties- Clinical trials) in patients with Primary Immunodeficiency Disease (PID). Nineteen patients (aged 18 to 69 years) participated in the pharmacokinetic assessment (see **Table 4**). The median half-life of Intragam® 10 in patients with PID was 34 days. This half-life may vary from patient to patient. IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Table 4: Pharmacokinetic parameters of Intragam® 10 in 19 PID patients

Parameter	Median (Range)
C_{max} (peak, g/L)	17.4 (11.9–21.4)
C_{min} (trough, g/L)	7.8 (4.9–11.3)
$t_{½}$ (days)	34.0 (25.0–50.6)

C_{max}, maximum serum IgG concentration.
C_{min}, trough (minimum) serum IgG concentration.
$t_{½}$, elimination half-life of IgG.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with Intragam® 10.

Carcinogenicity

No carcinogenicity studies have been conducted with Intragam® 10.

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. Do not return to refrigeration.

Protect from light.

Do not use after the expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

The following presentations in **Table 5** are registered for Intragam® 10.

Table 5: Presentations

Amount of IgG (g)	Volume of solution (mL)	Vial size (mL)
2.5	25	50
5	50	50
10	100	100
20	200	250

Note that not all presentations may be available.

Intragam® 10 is packaged in latex free materials.

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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Distributed by

Australian Red Cross Lifeblood

9 DATE OF FIRST APPROVAL

1 April 2011

10 DATE OF REVISION

21 April 2020

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Precaution to ensure adequate hydration added to thrombotic events. Use in the elderly section updated to include subjects from the post-authorisation safety study.
4.8	Updated with post-authorisation safety study
4.9	Cardiac impairment added as a risk factor
5.1	Updated with post-authorisation safety study
6.4	Instruction added to not return medicine to refrigeration post-removal from refrigeration and storage below 25°C