NZBLOOD
Te Ratonga Toto O Aotearoa

Biotherapies for Life™ CSL Behring

Life back in their hands[1–3]

evogam

Human Normal Immunoglobulin 16% (16g/100ml) – Subcutaneous

New Zealand's own **SC**Ig[1]

New Zealand's own SCIg[1]

New Zealand plasma.
New Zealand self-sufficiency.[1,4,5]

EVOGAM® is manufactured from plasma donated by New Zealand's voluntary, non-remunerated blood and plasma donors, collected by the New Zealand Blood Service.[1]

In accordance with WHO recommendations and to optimise security of supply for our remote nation, New Zealand has a policy of aiming for self-sufficiency in essential plasma-derived therapies such as immunoglobulins used in the treatment of a range of life threatening and debilitating conditions.[4,6,7]

CSL Behring employs state-of-the-art, chromatographic fractionation technology at its purpose-built facility, and continuously strives to maximise the amount of immunoglobulin extracted from every litre of plasma.[4,6]

EVOGAM® is the latest evolution of CSL Behring's immunoglobulin offering, fractionated for New Zealand from New Zealand's own plasma.

Read on for important information about EVOGAM – New Zealand's own SCIg[1]

SCIg = subcutaneous immunoglobulin

Introducing EVOGAM

EVOGAM is the first immunoglobulin formulated specifically for subcutaneous administration made from New Zealand's own plasma. EVOGAM provides immunoglobulin replacement therapy for patients in New Zealand who prefer this treatment option.[1,2]

EVOGAM is manufactured using the same core chromatographic plasma fractionation process used to manufacture INTRAGAM P, which CSL Behring has supplied in New Zealand since 2000.[1,4–6]

EVOGAM – a subcutaneous alternative to intravenous immunoglobulin (IVIg)[1]:

- **A 16% Ig concentration.**
- **Specifically formulated for subcutaneous injection.**
- **Approved for patients to self administer at home.**

EVOGAM is indicated for replacement therapy in adults and children for[1]:

- primary immunodeficiency disease (PID)
- symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

Optimising purity and pathogen safety[1]

The chromatographic plasma fractionation process used to manufacture EVOGAM includes multiple approaches to optimise the purity and pathogen safety of the final product.[1,4]

Optimising product purity[1]

- EVOGAM is manufactured to retain the key Fc and Fab IgG characteristics of human plasma.
- At least 98% of the protein present in EVOGAM is IgG.
- EVOGAM contains only trace amounts of IgA (typically <0.025mg/mL).

Optimising pathogen safety[1,4,8]

A number of processes and steps are incorporated in the manufacturing process for EVOGAM specifically to optimise pathogen safety, including:

- Testing of each blood and plasma donation by the New Zealand Blood Service before plasma is sent to CSL Behring for fractionation, to minimise the risk of pathogens entering the starting plasma pool.
- Screening of each plasma pool using nucleic acid amplification testing (NAT) at CSL Behring.

The EVOGAM manufacturing process also incorporates two dedicated and complementary pathogen reduction (inactivation and removal) steps to reduce the theoretical risk of pathogens being present in the final product. These steps are effective against HIV, HBV, HCV, HAV and parvovirus B19[1]:

1. *Pasteurisation.*
2. *Nanofiltration.*

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Clinical efficacy

The clinical efficacy and safety of EVOGAM has been assessed in[1,2,9]:

- A 36-week, phase lll, open-label, multi-centre clinical trial enrolling patients aged >3 years with primary immunodeficiency disease (n=35).
- An open-label extension study (reported results of a 2-year interim analysis).

EVOGAM provides effective protection against infections in patients requiring Ig replacement therapy[1,2]

Low rates of infection, absenteeism and hospitalisation with EVOGAM[1–3]

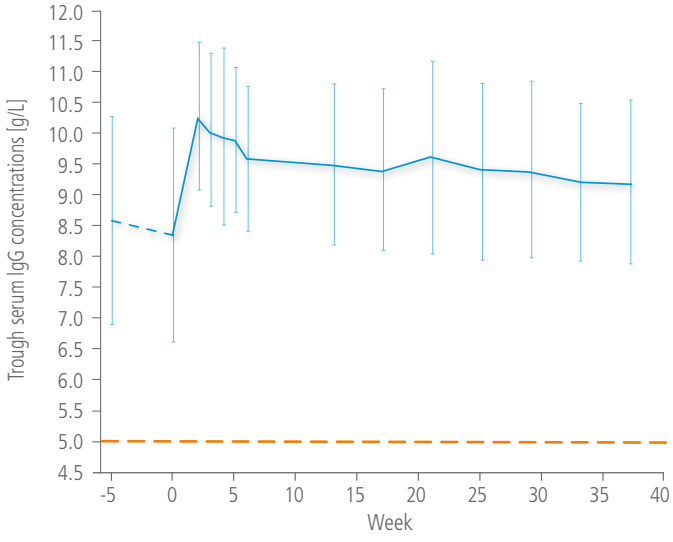
- No serious bacterial infections were reported.
- 2.8 infections per patient year.
- 2.97 days of missed school or work per patient year.
- 0.56 days of hospitalisation due to infection per patient year.

IgG trough levels were maintained following 1:1 (grams) transition from IVIg therapy[1,2]

Following transition from IVIg therapy, EVOGAM maintained trough levels using a 1:1 dose conversion[1,2]

- Consistent therapeutic Ig levels were achieved with EVOGAM.[1,2]
- The mean trough IgG concentration with SCIg was higher than with previous Ig treatment (8.94 versus 8.27g/L, p = 0.0063).[1]
- Trough IgG concentrations of ≥5g/L were maintained in all patients throughout the study.[1,2]
- Steady state was achieved from visit 6 (Week 13) onwards, with minimal difference between peak and trough IgG levels.[1,2]

Mean trough serum IgG concentrations over time (n=35)[2]



Study Design:[2]

Thirty-five PID patients previously treated with IVIg (n=34) or SCIg (n=1) received EVOGAM weekly for 36 weeks, using a 1:1 dose conversion from IVIg to SCIg. Primary endpoints were serious bacterial infections (SBIs) and steady-state serum immunoglobulin G (IgG) trough concentrations. Secondary endpoints included adverse events, infection episodes, antibiotic use, days off work/school, hospitalisation, pharmacokinetics and quality of life.

Safety and tolerability

Contraindications

EVOGAM is contraindicated in patients who have had an anaphylactic reaction to the active substance or to the excipient glycine.[1]

Injection site tolerability[1,2]

- Injection site reactions are common with EVOGAM, and are mostly mild to moderate in intensity.
- Symptoms commonly occurred within 8 to 12 hours of the injection, and usually resolved within 72 hours without intervention.
- Symptoms improved over the duration of the study, with a decrease in both the number and severity of symptoms over time.

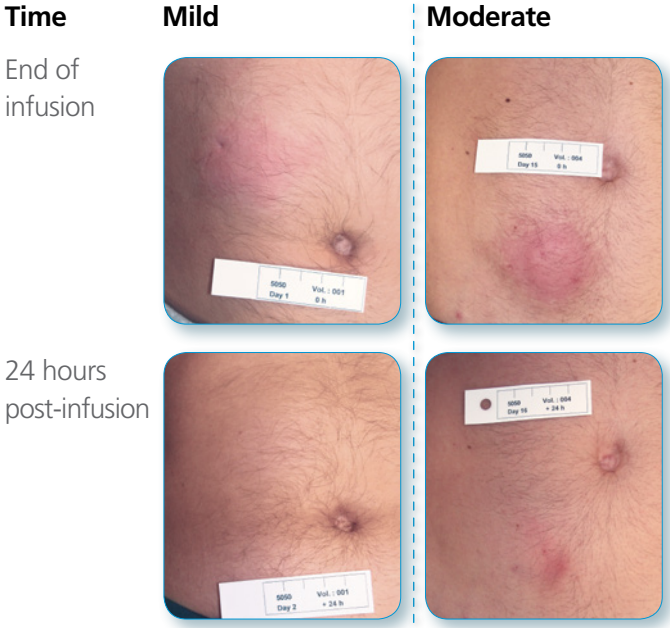
Adverse events are usually mild to moderate[1,2]

- In the phase III clinical trial of EVOGAM's safety and efficacy:
  - there were no withdrawals from the clinical trial due to adverse events
  - the incidence of systemic adverse events was low
  - the majority of adverse events with EVOGAM were mild to moderate in intensity
  - headache was the most frequently reported adverse event, in 23% of patients, at a rate of 0.031 per injection (1 in 32). All headaches were mild to moderate in intensity

Hypersensitivity reactions to immunoglobulins are rare[1,10]

EVOGAM contains traces of IgA, which infrequently may provoke anaphylaxis in IgA deficient patients who have anti-IgA antibodies.[1]

Injection site reactions over time



* Images of injection sites following SCIg administration. CSL Behring.

Other precautions for use[1]

Aseptic meningitis syndrome, thromboembolism, haemolysis, and renal dysfunction have been reported to occur infrequently in association with human immunoglobulin administration.

For a full list of precautions, please refer to the EVOGAM Data Sheet

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New Zealand's own SCIg[1]

EVOGAM:
Dosage and administration information[1,2,11,12]

EVOGAM IS FOR SUBCUTANEOUS USE ONLY

It must **NOT** be administered intravenously.

- The recommended initial administration rate for injection is 10mL/hour.
- The subsequent injection rate may be increased as tolerated up to 20mL/hour.
- For EVOGAM volumes >20mL, administration in divided doses at different injection sites is recommended.
- EVOGAM may be infused at multiple sites simultaneously if desired, to minimise infusion time.
- Administration methods for SCIg include use of an infusion pump, or rapid push techniques. The choice of administration technique and equipment is at the discretion of the treating healthcare professional.

Note: On 1 January 2013 CSL Biotherapies (Broadmeadows) became CSL Behring. Product packaging will be updated to reflect this change upon receipt of Regulator approval.

Dose and dosage interval must be individualised based on IgG trough levels and clinical response[1]

- A weekly dose in the range of 0.05–0.15g/kg body weight is recommended. This corresponds to a total monthly dose of EVOGAM in the range of 0.2–0.6g/kg.
- This method of dose calculation may be used for patients commencing immunoglobulin replacement therapy with EVOGAM.

Transitioning from IVIg to EVOGAM[1,2]

- For patients transitioning from IVIg, a 1:1 dose (grams) transition is recommended.[1] This is calculated as the cumulative monthly dose divided by 4 to gain the weekly dose.
- In the PID study, patients transitioning from IVIg had their first EVOGAM injection 2 weeks after the last injection of IVIg.

Dosing of EVOGAM[1]

There are two methods for calculating the dose of EVOGAM[1,2]

1. Calculating EVOGAM dose from body weight (g/kg)

Patients body weight (kg)	x	Target dose per kg from range 0.05–0.15g	=	EVOGAM weekly dose (grams)
e.g. 70kg	x	0.10g / kg	=	7g

2. Calculating EVOGAM dose for patients transferring from IVIg

IVIg dose (grams)	÷	Treatment interval (weeks)	=	EVOGAM weekly dose (grams)
e.g. 28g	÷	4 weeks	=	7g

Injection volume of EVOGAM[1]

Calculating EVOGAM injection volume from dose in grams

1. Calculate EVOGAM dose as shown above
2. Use equation below to convert dose in grams to injection volume

EVOGAM dose (grams)	x	6.25*	=	EVOGAM weekly injection volume (mL)
e.g. 7g	x	6.25	=	44mL

* Derived from the concentration of EVOGAM 16% (1 gram of immunoglobulin in 6.25mL)[1]

Dosing calculator available from CSL Behring.

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Administration directions for Health Care Practitioners

Step 1: Equipment Preparation

a) **Remove** EVOGAM from fridge and allow to reach room temperature.

b) **Gather** required equipment.

c) **Check** vial for particulates, expiry date. Do not shake.

d) **Wash** hands.

e) **Clean** vial stopper with alcohol swab.

Step 2: Prepare vial adaptor

a) **Remove** the top cover of the vial adaptor, leaving the adaptor inside the blister pack.

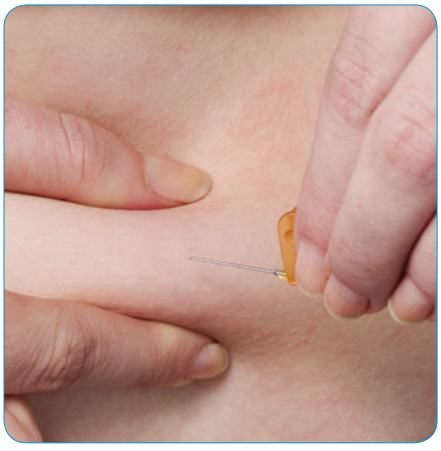
b) **Place** the EVOGAM vial on a flat surface.

c) **Place** the vial adaptor over the top of the vial, using the blister pack to handle the vial adaptor. Press down firmly until the vial adaptor snaps into place, so that it pierces the rubber stopper.

d) **Remove** the outer package of the vial adaptor and discard.

Step 3: Prepare syringe

Pull back the plunger to draw air into syringe. The volume of air should be the same as the volume of Evogam liquid to be withdrawn from the vial.



Step 7: Insert needle

a) **Select** an appropriate subcutaneous injection site or sites.

b) **Clean** the site with an alcohol wipe or as per hospital protocol.

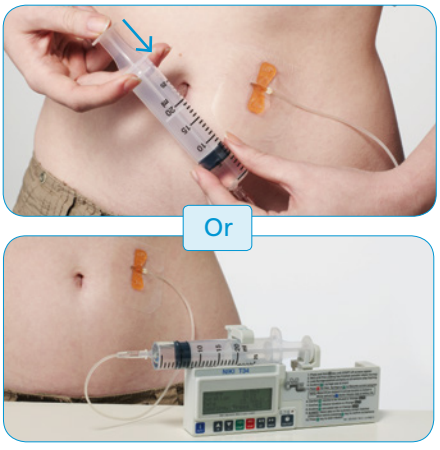
c) **Insert** needle. For children and small adults a 45° angle may be preferable to a 90° angle.

d) **Secure** needle with tape or dressing.

Step 8: Check needle placement

a) **Draw** back on the plunger and check for absence of blood return, to confirm subcutaneous placement.

b) **Continue** with infusion if no blood is present. If blood is present, remove and discard needle and tubing and repeat from step 6.



Step 9: Start Infusion

Administer EVOGAM according to prescribed method, using an infusion pump, or via a slow push technique. The recommended initial infusion rate is 10mL/hr per site, with subsequent infusion rate increased as tolerated to a maximum of 20mL/hr per site. For volumes >20mL, administration in divided doses at different injection sites is recommended.

Step 4: Connect to vial

a) **Attach** the syringe to the vial adaptor by twisting the syringe onto the connection.

b) **Inject** air into the airspace of vial.

Step 5: Withdraw Evogam from vial

a) **Invert** the vial and syringe, and withdraw the desired volume of EVOGAM into the syringe.

b) **Twist** syringe to detach from vial adaptor.

c) **Repeat** steps when multiple vials are required for desired dose, using a new vial adaptor for each vial.

Step 6: Prepare the infusion tubing

Connect the injection tubing to the syringe containing EVOGAM, and prime the tubing.

Step 10: After the infusion

a) **Remove** needle and dressing, and dispose of waste as required.

b) **Document** EVOGAM treatment in medical records, including batch number.

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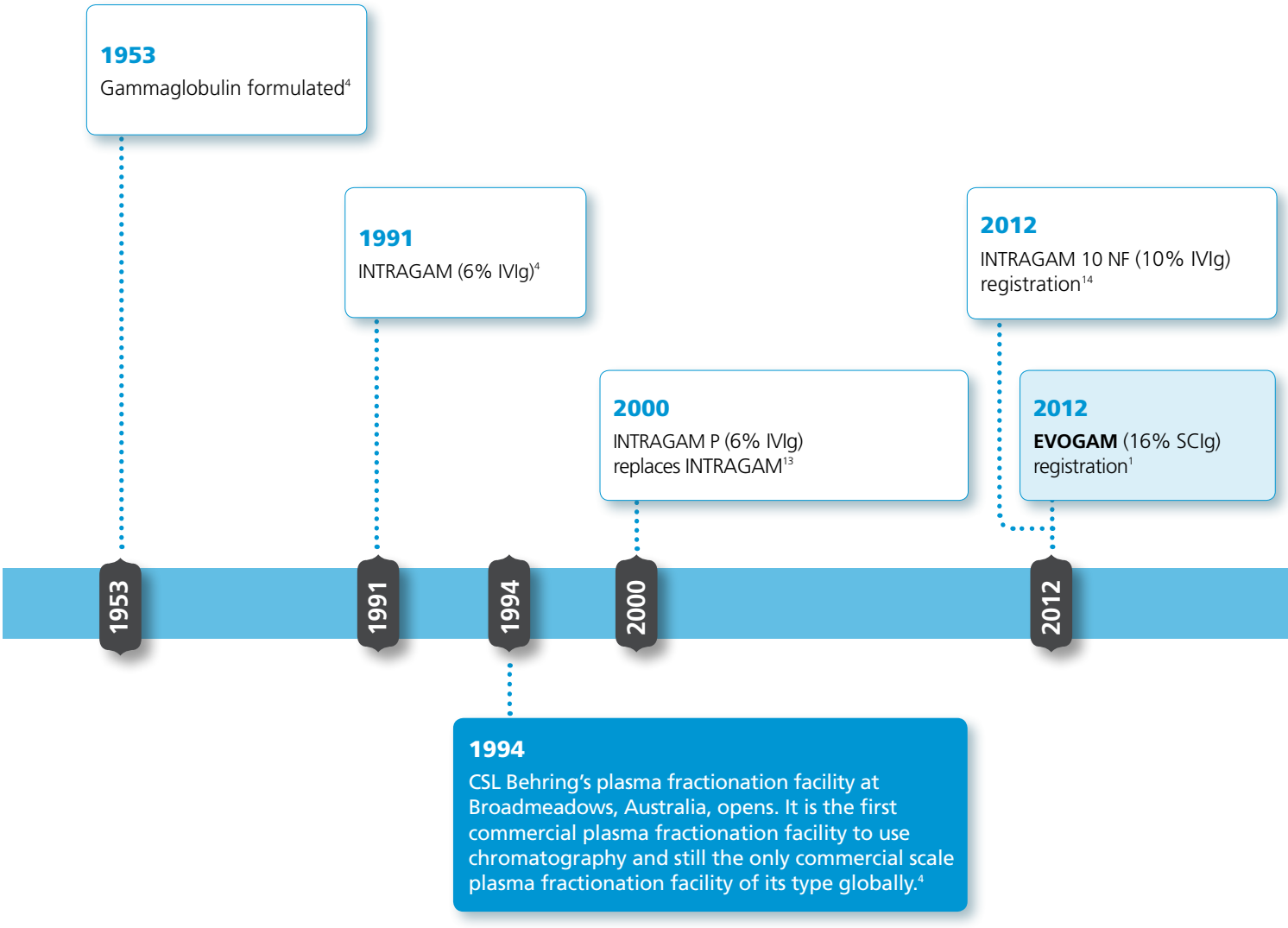
CSL Behring: Manufacturing immunoglobulin products since 1953[4]

As New Zealand's chosen national fractionator, CSL Behring has a proud history of manufacturing life-saving products from New Zealand's plasma. CSL Behring is focused on ensuring yield is optimised – making every drop of New Zealand's plasma count.[4,5]



Immunoglobulins
IVIg = intravenous
SCIg = subcutaneous

Presentation and storage[1]

- Convenient packaging:
  - EVOGAM is packaged in latex-free materials.
- Storage:
  - Store at 2°C to 8°C. (Refrigerate. Do not freeze.)
  - EVOGAM can be stored at room temperature (below 25°C) for 2 weeks prior to use.

0.8g in 5mL **3.2g in 20mL**

Note: On 1 January 2013 CSL Biotherapies (Broadmeadows) became CSL Behring. Product packaging will be updated to reflect this change upon receipt of Regulator approval.

Before prescribing please review Data Sheet. The Data Sheet can be accessed at www.cslbehring.com.au/nz-pi.

EVOGAM® (Human Normal Immunoglobulin 16% (16g/100mL)). **Indications:** Replacement therapy in adults and children in primary immunodeficiency disease and symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. **Contraindications:** Patients who have had a true anaphylactic reaction to the active substance or to the excipiewnt glycine. **Precautions:** EVOGAM® must not be administered intravenously. If EVOGAM® is inadvertently administered into a blood vessel, patients could develop shock. EVOGAM® should be used with caution in patients with known allergy to constituents of the preparation. EVOGAM® contains traces of IgA which seldomly may provoke anaphylaxis in IgA deficient patients with anti-IgA antibodies. Aseptic meningitis syndrome, renal dysfunction, acute renal failure, thrombotic events, haemolysis have been reported in association with Ig treatment, and may occur with subcutaneous Ig treatment. Products such as EVOGAM® 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, and by dedicated virus removal and inactivation procedures included in the manufacturing process. For all precautions and risk factors review approved Data Sheet. **Interactions:** EVOGAM® may affect the response to live attenuated vaccines. **Adverse Effects:** Reported adverse events include headache, nausea, diarrhoea, vomiting, fever, hypotension, and arthralgia. Infusion site reactions were common, mostly mild to moderate, and reduced over time. For all adverse events review approved Data Sheet. **Dosage & Administration:** EVOGAM® is to be administered via the subcutaneous route. Do not administer intravenously. A common weekly dose is 0.05-0.15 g/kg body weight. Recommended initial infusion rate is 10 mL/hour which can be increased after the first infusion to 20 mL/hour as tolerated. When large doses (>20mL) are given, divided doses at different sites are advised. **Classification:** Prescription Medicine. Based on EVOGAM® Data Sheet, date of preparation: May 2012 (V12/12).

REFERENCES: 1. EVOGAM Approved Data Sheet, date of preparation May 2012. **2.** Empson M *et al.* J Clin Immunol 2012;32:897–906. **3.** Gardulf A. BioDrugs 2007;21(2):105–116. **4.** Plasma Fractionation Review Committee (Philip Flood, Chairman). Review of Australia's Plasma Fractionation Arrangements. Canberra: 2006. **5.** National Blood Authority Australia. CAFA Agreement.2010. (cited 22 Jan 2013). Available from www.nba.gov.au/supply/cafa.pdf. **6.** National Blood Authority Australia. Annual Report 2011–2012. (cited 22 Jan 2012). Available from www.nba.gov.au/pubs/annual-report.html. **7.** WHO Expert Group. Vox Sang 2012;103:337–342. **8.** Australian Red Cross Blood Service. Blood collection and testing; (Updated 23 December 2011; cited 28 February 2012). Available from www.transfusion.com.au/blood_products/collection_testing. **9.** Stephens S *et al.* 22nd Annual Scientific Meeting, Australasian Society of Clinical Immunology & Allergy; 2011: Wellington. **10.** Caress J *et al.* Expert Opin Drug Saf 2010;9(6):971–979. **11.** Berger M. Clinical Focus on Primary Immune Deficiencies: Subcutaneous IgG therapy in Immune Deficiency Diseases. 2008;13:1–12. **12.** Shapiro R. J Clin Immunol 2010;(30):301–307. **13.** INTRAGAM P Approved Data Sheet, date of preparation August 2012. **14.** INTRAGAM 10 NF Approved Data Sheet, date of preparation August 2012.

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0.8g in 5mL **3.2g in 20mL**

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CSL Behring is committed to the development and provision of high quality product education and support materials to assist the appropriate use of the plasma-derived therapies we manufacture for the New Zealand Blood Service. CSL Behring willingly complies with the ASA Code of Practice (www.asa.co.nz) which defines New Zealand's standards for the content of therapeutic product education and support materials.

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NZBLOOD Te Ratonga Toto O Aotearoa

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