NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Evogam® (16% (16 g/100 mL)), solution for subcutaneous injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Normal Immunoglobulin

Evogam® is a 16% solution containing 16 g/100 mL of human plasma protein of which at least 98% is immunoglobulin G (IgG). At least 85% consists of monomers and dimers (typically >90%) and <10% of the IgG are aggregates.

The distribution of the IgG subclasses closely resembles that found in normal human plasma (approximate ranges for Evogam®: 47.8–58.1% IgG_1, 38.8–49.3% IgG_2, 0.9–1.4% IgG_3, 1.4–2.1% IgG_4).

Evogam® contains only trace amounts of IgA, typically <0.025 mg/mL.

Evogam® is manufactured from human plasma donated by New Zealand's voluntary and non-remunerated donors.

Evogam® contains 2.25 g of glycine per 100 mL as a stabiliser.

Evogam® contains no preservatives.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for subcutaneous administration.

The solution is clear and colourless or pale-yellow or light brown.

The pH value of the ready-to-use solution is 5.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Evogam® is indicated in adults and children for replacement therapy in:

- Primary Immunodeficiency Diseases (PID) and

- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment

4.2 Dose and method of administration

Treatment should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Dose

The dose and dosage interval must be individualised for each patient based on their measured IgG trough levels and ongoing clinical response. The following dose regimens are given as a guideline.

A weekly dose in the range 0.05–0.15 g/kg body weight is recommended (this corresponds to a total monthly dose of Evogam® in the range of 0.2–0.6 g/kg body weight).

As the dose is given by body weight and adjusted to clinical outcome, the dose in the paediatric population is not considered to be different to that of adults.

Paediatric population

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Method of administration

Evogam® must be administered **SUBCUTANEOUSLY**. Evogam® **MUST NOT** be administered intravenously**.**

Evogam® must be administered via the subcutaneous route, preferentially into the upper outer arms/upper thighs, abdomen, and/or lateral hip.

A common Evogam® weekly dose is 0.05–0.15 g (approximately 0.3–0.9 mL) per kg body weight, which may be administered at several infusion sites. When large doses are given (>20 mL), it is advisable to administer them in divided doses at different sites.

Infusion rate

The recommended initial infusion rate is 10 mL/hour per site. The infusion rate may be gradually increased after the first completed infusion up to 20 mL/hour per site as the patient's tolerability and comfort allows. The maximum dose administered during clinical trials was 40 mL/hour using two infusion pumps simultaneously.

Subcutaneous infusion for home treatment

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

If the supervising physician believes that home administration is appropriate, the patient or caregiver must be instructed and trained in: subcutaneous administration techniques; the keeping of a treatment diary; recognition of and measures to be taken in the case of severe adverse reactions.

For further information on special precautions for disposal and other handling, see section 6.6.

4.3   Contraindications

Evogam® is contraindicated in patients with a history of a true anaphylactic reaction to the active substance or to any of the components (e.g. glycine) (see section 4.4).

4.4   Special warnings and precautions for use

Route of administration

Evogam® must be administered subcutaneously. Evogam® **Must Not** be administered intravenously. It has not been studied for intravenous or intramuscular use.

If Evogam® is inadvertently administered into a blood vessel, patients could develop shock. In the case of shock, current medical standards for shock treatment should be observed.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time, are switched from an alternative product, or, in rare cases, when there has been a long interval since previous infusion.

Hypersensitivity

True hypersensitivity reactions to immunoglobulins are rare. Evogam® should be used with caution in patients with a known allergy to constituents of the preparation.

Evogam® contains traces of IgA which rarely may provoke anaphylaxis in IgA deficient patients with anti-IgA antibodies. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG product remains the only option, should be treated with Evogam® under close medical supervision.

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 an anaphylactic reaction, the infusion should be stopped immediately and appropriate treatment initiated.

Thromboembolic events

There is clinical evidence of an association between human immunoglobulin administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses. Caution should be exercised in prescribing and administering Evogam® in patients with pre-existing risk factors for thromboembolic events such as advanced age, estrogen use, in-dwelling vascular catheters, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), and a history of venous or arterial thrombosis, patients with acquired or inherited hypercoagulable states, patients with prolonged periods of immobilisation, severely hypovolaemic patients and patients with hyperviscosity (including cryoglobulins, fasting chylomicronaemia and/or high triglyceride levels, and monoclonal gammopathies).

In patients at risk for thromboembolic adverse reactions, Evogam® should be administered subcutaneously at the minimum rate of infusion and dose possible based on clinical judgement, and these individuals should be monitored for thromboembolic complications. Consideration should also be given to measurement of baseline blood viscosity in individuals at risk of hyperviscosity.

Aseptic Meningitis Syndrome (AMS)

An Aseptic Meningitis Syndrome (AMS) has been reported to occur infrequently in association with human immunoglobulin administration. The syndrome usually begins within several hours to two days following immunoglobulin 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) immunoglobulin treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Reactions reported to have occurred with intravenous immunoglobulin treatment

The following reactions have been reported to occur with intravenous immunoglobulin (IVIg) treatment and may occur with subcutaneous immunoglobulin (SCIg) treatment:

Haemolysis

Evogam® 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 immunoglobulin therapy due to enhanced red blood cells (RBC) sequestration. The following risk factors are associated with the development of haemolysis: high cumulative doses, non-O blood groups, and underlying inflammatory conditions. Evogam® 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 and discontinuation of the IgG treatment should be considered by the treating physician, if haemolysis develops.

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

Renal function should be monitored in patients at increased risk of developing acute renal failure. If renal function deteriorates, IgG treatment discontinuation should be considered.

While these reports of renal dysfunction and acute renal failure have been associated with the use of IVIg products containing excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. Evogam® contains glycine but it does not contain sucrose, maltose or glucose.

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

Pathogen safety

Evogam® is manufactured 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, two dedicated pathogen reduction steps are included in the manufacturing process of Evogam® to reduce the possibility of pathogen transmission. These are pasteurisation (heating at 60°C for 10 hours) and nanofiltration. These steps are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and the non-enveloped hepatitis A virus (HAV) and parvovirus B19. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety. Evogam® 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 (e.g. hepatitis A and hepatitis B) should be considered where appropriate, for patients in receipt of medicinal products manufactured from human plasma.

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

Genotoxicity and carcinogenicity

No carcinogenicity or genotoxicity studies have been conducted with Evogam®.

4.5   Interaction with other medicines and other forms of interaction

Vaccinations with 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 Evogam®, 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.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this product for use in human pregnancy has not been established in controlled clinical studies. Evogam® should be given to pregnant women only if clearly needed.

Breast-feeding

The safety of this product for use during lactation has not been established in controlled clinical studies. Immunoglobulins are excreted in breast milk and may contribute to the transfer of protective antibodies to the neonate.

Fertility

No reproductive toxicity studies have been conducted with Evogam®.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Patients naive to immunoglobulin may experience a higher frequency of adverse effects including those of a minor nature.

Rarely, human normal immunoglobulins may cause allergic reactions and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration (see section 4.4). In case of severe reactions, the infusion should be stopped and appropriate treatment initiated.

Rare cases of thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses, and cases of reversible aseptic meningitis have been observed with human normal immunoglobulin.

Experience from clinical studies

Table 1 summarises treatment related adverse reactions (ARs) identified in clinical studies of Evogam® in 49 individual subjects, of whom 41 were adults and 8 children, from a total of 5694 subcutaneous infusions.

The ARs reported in **Table 1** are summarised and categorised according to the MedDRA System Organ Class and frequency. Frequency per infusion has been evaluated using the following criteria: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), and rare (≥1/10,000 to <1/1000).

Table 1: Adverse Reactions Reporting Rate per Infusion

MedDRA System Organ Class	Frequency of ARs reflected by Preferred Terms (PT)	
	Very common (≥1/10)	**Common(≥1/100 and <1/10)**
Nervous system disorders	Headache	-
Vascular disorders	-	Hypotension
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, abdominal pain	-
Musculoskeletal and connective tissue disorders	Pain in extremity	Back pain, arthralgia, myalgia
General disorders and administration site conditions	Infusion site reactions[a], fever[b]	Chills, fatigue

[a] Group term includes PTs of ARs at infusion/injection site: pain, haematoma, pruritus, warmth, erythema, and induration.

[b] Group term includes PTs of pyrexia, body temperature increased.

Local tolerability reactions at the infusion site were also assessed in the clinical studies with Evogam®. Most subjects reported pain, pruritus, or warmth, erythema, and/or induration being present between 8–12 hours after the infusion. At 72 hours after infusion, the frequency of reported symptoms had markedly decreased. The incidence of all reported tolerability reactions at the infusion site were reported less frequently over the length of the study. The majority of these symptoms reported were of mild or moderate intensity.

Paediatric population

Evogam® was evaluated in 8 children ≤13 years in the clinical studies. There were no apparent differences in the safety and efficacy profiles as compared to adults. No paediatric-specific dose adjustments were necessary to achieve the desired serum IgG levels. The safety and efficacy of Evogam® was not studied in the paediatric population under 5 years of age.

Elderly

Clinical studies of Evogam® did not include sufficient numbers of patients aged 65 years and over to determine whether safety of this product is different in this population.

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

Consequences of an overdose are not known.

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

Evogam® contains functionally intact IgG with a broad spectrum of antibodies against infectious agents. It has an IgG subclass distribution closely proportional to normal human plasma. The IgG molecules have not been chemically or enzymatically modified and the Fc and Fab functions are retained. Evogam® contains the IgG antibodies present in the donor population. It is prepared from pooled plasma collected from not fewer than 1000 donors.

The manufacturing process contains two dedicated and complementary steps to reduce the possibility of pathogen transmission: pasteurisation (60°C for 10 hours) and nanofiltration (see section 4.4/Pathogen safety).

Mechanism of action

Adequate doses of human normal immunoglobulin restore abnormally low IgG levels to the normal range.

Clinical efficacy and safety

The pivotal open-label, prospective, multicentre clinical study conducted in Australia and New Zealand evaluated the efficacy, pharmacokinetics, safety, tolerability and quality of life of Evogam® in adult and paediatric subjects with PID. Thirty adult and five paediatric PID subjects, who had been previously treated either with intravenous immunoglobulin (IVIg) monthly (n = 34) or with normal immunoglobulin administered subcutaneously (SCIg; n = 1), were treated with weekly subcutaneous infusions of Evogam® for 9 months, at a planned weekly dose calculated to be equivalent to one quarter of the cumulative monthly dose of IVIg (between 0.2–0.6 g/kg/month).

Subjects received a mean weekly dose of 6.83 g (range 3.0–13.5 g), infused subcutaneously via a mean of 2.63 infusion sites (range: 1.0–5.0), over an average duration of 1.53 hours (range: 0.9–2.7 hours).

The primary endpoint was the annual rate of serious bacterial infections (SBIs) including bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess (to a pre-specified upper 99% confidence limit of 1%). The annualised rate of SBI was 0 infections per subject per year for both the per protocol and intention to treat populations, with 99% upper confidence limits of 0.36 and 0.33, respectively. This data is based on the Efficacy Period (weeks 13–36).

The annual rate of any infections, a secondary endpoint, was 2.80 infections per subject per year.

IgG concentrations were at steady state during the efficacy phase of the study and a repeated measures analysis showed that mean trough concentration of IgG in subjects treated with Evogam® (9.11 g/L, 95% CI: 8.68–9.55 g/L) was higher than in their previous treatment (8.30 g/L, 95% CI: 7.82–8.80 g/L; p = 0.0021).

The change from baseline health and treatment related quality of life was assessed in 27 subjects by the SF-36v2™ and Life Quality Index (LQI) questionnaires. SF-36v2™ results showed a similar health-related quality of life on both the previous treatment and Evogam®. LQI scales showed significant improvement in treatment interference and therapy setting, indicating preference for home based SCIg treatment.

Following the pivotal study, an open-label multicentre extension study was conducted (n = 41) in 34 (82.9%) adult and 7 (17.1%) paediatric subjects. The age ranges were 5.9–11.7 in the paediatric group (mean 9.89) and 14.1–68.6 in the adult group (included adolescents; mean 45.25). The primary objective was to assess the safety and tolerability of Evogam® in subjects requiring Ig replacement therapy who had either completed the pivotal clinical trial (n = 27), or had switched from alternative IVIg (n = 13) or SCIg (n = 1) therapy. The secondary objective was to monitor serum IgG trough levels, as a surrogate measure of Evogam® efficacy in patients with PID. The median duration of treatment was 589.0 days in subjects who switched from previous IVIg therapy and 891.5 days in subjects who transferred from the pivotal study.

At baseline, the mean serum IgG trough level for the 41 enrolled subjects was 9.02 g/L (range: 5.0–13.3). During the treatment period the mean serum IgG trough level was maintained above 8 g/L; based on data from 35 subjects. At the individual subject level, 34 (out of 35) subjects for whom trough level data was available, had IgG trough levels at clinically desirable levels (i.e. ≥5 g/L).

5.2 Pharmacokinetic properties

Absorption and Distribution

Following subcutaneous administration of Evogam®, peak serum levels are achieved after approximately 8.4 hours.

In a clinical trial with Evogam® (n = 31), subjects achieved sustained trough levels (mean 9.11 g/L) over a period of 24 weeks when receiving weekly doses in the range of 0.05–0.15 g/kg.

The pharmacokinetic (PK) parameters of Evogam® were evaluated in a subset of 23 subjects (aged 27 to 67 years) with Primary Immunodeficiency Diseases (PID) (refer to **Table 2**). A peak IgG concentration of 8.87 g/L and a trough IgG concentration of 8.32 g/L were observed during the 7 day PK evaluation period.

Table 2: Pharmacokinetic parameters of Evogam® in 23 PID subjects

Parameter	Mean (Range)
C_{max} (peak, g/L)	8.87 (6.70–11.1)
C_{min} (trough, g/L)	8.32 (6.0–10.6)
T_{max} (days)	0.35 (0–1.0)
$AUC_{(0–t),\ ss}$ (day.g/L)	61.10 (44.78–80.79)
CL/F (L/day)	0.119 (0.071–0.291)
$T_{1/2}$ (days)[a]	54.6 (13.65–164.87)

C_{max}; maximum serum IgG concentration, C_{min}; trough (minimum) serum IgG concentration, T_{max} time to maximum serum IgG concentration, $AUC_{(0–t),\ ss}$ area under the curve over a dosing interval at steady state, CL/F apparent clearance (dose/$AUC_{(0-t),\ ss}$), $T_{1/2}$ terminal half-life, [a] terminal half-life in 18 subjects.

Elimination

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Paediatric population

No differences were seen in the pharmacokinetic parameters between adult and paediatric study patients.

5.3   Preclinical safety data

IgG are normal constituents of the human body.

6 PHARMACEUTICAL PARTICULARS

6.1   List of excipients

Glycine
Water for injections

6.2   Incompatibilities

Evogam® must not be mixed with other medicinal products.

For interactions with live attenuated virus vaccines: see section 4.5.

6.3   Shelf life

2 years

Shelf life after opening:

Use in one patient on one occasion only.

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

6.4   Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Do not use if the solution has been frozen.

Once removed from refrigeration, store below 25°C and use within 2 weeks.

Protect from light.

For storage conditions after first opening of Evogam®, see section 6.3.

6.5 Nature and contents of container

Solution in a single glass vial, with a rubber stopper, an aluminium seal and a plastic flip-top cap.

Evogam® is packaged in latex free materials.

Pack sizes:

- One vial of 5 mL solution containing 0.8 g human normal immunoglobulin.
- One vial of 10 mL solution containing 1.6 g human normal immunoglobulin.
- One vial of 20 mL solution containing 3.2 g human normal immunoglobulin.

Not all registered presentations may be supplied.

6.6 Special precautions for disposal and other handling

Evogam® should be brought to room temperature before use.

If Evogam® appears to be turbid or to contain sediment, it must not be used. The unopened bottle should be returned to the New Zealand Blood Service.

Any unused portion should be discarded appropriately.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

20 December 2012

10 DATE OF REVISION OF THE TEXT

3 June 2021

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Clarification of infusion rate
4.4	Updated for consistency with other IVIg products.