

Product Information

EVOGAM[®]

Australia

NAME OF THE MEDICINE

Human Normal Immunoglobulin 16% (16 g per 100 mL) solution for subcutaneous administration.

DESCRIPTION

Evogam[®] is a sterile solution containing 16 g per 100 mL of total human plasma immunoglobulin with a purity of at least 98% immunoglobulin G (IgG). At least 85% consists of monomers and dimers (typically > 90%) and less than < 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% IgG₁, 38.8-49.3% IgG₂, 0.9-1.4% IgG₃, 1.4-2.1% IgG₄).

The pH value of the ready-to-use solution is 6.6. Evogam contains 2.25 g of glycine in each 100 mL as a stabiliser which is a physiological non-essential amino acid. Evogam does not contain a carbohydrate stabiliser (eg. sucrose, maltose) and contains no preservative. Evogam contains only trace amounts of IgA, typically <0.025mg/mL.

Evogam is manufactured from human plasma collected by the Australian Red Cross Blood Service.

The manufacturing process contains two dedicated steps to reduce the possibility of pathogen transmission:

- pasteurisation (heating at 60°C for 10 hours)
- nanofiltration

PHARMACOLOGY

Pharmacodynamic properties

Evogam contains the IgG antibodies present in the donor population. It is prepared from pooled plasma collected from not fewer than 1000 donors. It has an IgG subclass distribution closely proportional to normal human plasma.

Evogam contains functionally intact IgG with a broad spectrum of antibodies against infectious agents. The IgG molecules have not been chemically or enzymatically modified and the Fc and Fab functions are retained.

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

Pharmacokinetic properties

The pharmacokinetic (PK) parameters of IgG and IgG subclasses in Evogam were established in 23 patients (aged 27 to 67 years) with primary immunodeficiency disease (PID). The PK phase of the clinical trial occurred during 6 months treatment with weekly dosing in the range

0.05 - 0.15 g/kg Evogam. 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.

Pharmacokinetic Parameters of Evogam in 23^a PID patients

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} ^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 patients .

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

CLINICAL TRIALS

Treatment of primary immunodeficiency disease (PID)

The pivotal open-label, prospective, multicenter clinical study conducted in Australia and New Zealand evaluated the efficacy, pharmacokinetics, safety, tolerability and quality of life of Evogam in adult and paediatric patients with PID. Thirty adult and five paediatric PID patients were treated with weekly subcutaneous administrations of Evogam for 9 months. Thirty four of these patients were previously treated monthly with intravenous immunoglobulin and one patient with normal immunoglobulin administered subcutaneously.

The planned weekly dose of Evogam was calculated to be equivalent to one quarter of the cumulative monthly dose of intravenous immunoglobulin (IVIg) of between 0.2 – 0.6 g/kg/month. Patients received a mean weekly dose of 6.83 g (range 3.0 to 13.5 g), (calculated in the first 3 months of treatment), infused via a mean of 2.63 infusion sites (range: 1.0 to 5.0), over an average duration of 1.53 hours (range: 0.9 to 2.7 hours).

The primary endpoint was the annual rate of serious bacterial infections (SBIs) including bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, visceral abscess to a pre-specified upper 99% confidence limit of 1%. The annualised rate of SBI was 0 infections per patient per year. During the Efficacy Period (weeks 13 - 36), the rate of SBIs per patient per year was 0 for both the Per Protocol (PP) and Intention to Treat (ITT) Populations with 99% upper confidence limits of 0.36 and 0.33, respectively.

The annual rate of any infections, a secondary endpoint, was 2.80 infections per patient 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 patients treated with Evogam (9.11 g/L, 95% CI: 8.68 to 9.55 g/L) was higher than their previous treatment (8.30 g/L, 95% CI: 7.82 to 8.80 g/L; p=0.0021).

Change from baseline health and treatment related quality of life was assessed in 27 patients by the SF36v2™ 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.

An additional clinical trial (an extension of the pivotal trial) is being conducted to assess the ongoing safety and tolerability with Evogam, as well as trough IgG concentrations in adult and paediatric patients with PID. An interim analysis was conducted on data from two children that did not participate in the pivotal clinical trial. The results from these two children (aged eight and ten years old) showed that adequate steady state trough IgG concentrations were achieved after 6 months treatment with Evogam. Results from all patients will be reported at the conclusion of this trial.

INDICATIONS

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

- Primary Immunodeficiency Disease (PID) and
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment

CONTRAINDICATIONS

Evogam is contraindicated in patients who have had a true anaphylactic reaction to the active substance or to the excipient glycine.

PRECAUTIONS

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 or, in rare cases, when there has been a long interval since previous infusion.

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 patient and the batch of the product.

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

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

Thromboembolism

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 obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients and patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, Evogam should be administered subcutaneously at the minimum rate of infusion and dose practicable.

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 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. Evogam recipients should be monitored for clinical signs and symptoms of haemolysis.

Renal Dysfunction

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.

In case of renal impairment, Evogam discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of 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. Evogam does not contain sucrose, maltose or glucose.

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

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. In addition, 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.

Effects on Fertility

No reproductive toxicity studies have been conducted with Evogam.

Use in 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.

Use in Lactation

The safety of this product for use in human pregnancy/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.

Paediatric Use

Evogam was evaluated in eight children \leq 13 years in clinical studies. There were no apparent differences in the safety and efficacy profiles as compared to adult patients. No paediatric-specific dose adjustments were necessary to achieve the desired serum IgG levels. The safety and efficacy of Evogam was not studied in paediatric patients under five years of age.

Use in the 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.

Carcinogenicity and Genotoxicity

No carcinogenicity or genotoxicity studies have been conducted with Evogam.

Interactions with Other Medicines

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.

The interaction of Evogam with other drugs has not been established.

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.

ADVERSE EFFECTS

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

The following treatment related reactions were identified in clinical studies of Evogam in 37 patients, which consisted of 29 adults and 8 children, from a total of 1216 subcutaneous infusions.

System organ class	Very common (³ 1/10)	Common (³ 1/100 and < 1/10)
Nervous system disorders	Headache	-
Gastrointestinal disorders	Nausea Diarrhoea Vomiting	-
General disorders and administration site reactions	Infusion site reactions* Fever [†]	Chills
Musculoskeletal and connective tissue disorders	-	Back pain Arthralgia
Vascular disorders	-	Hypotension

* Group term includes preferred terms (PTs) of infusion site pain, injection site haematoma, injection site pruritus

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

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 PRECAUTIONS). In case of severe reactions, the infusion should be stopped and appropriate treatment initiated. When large doses are given, it is advisable to administer them in divided doses at different sites.

Local tolerability reactions at the infusion site were also assessed in the clinical studies with Evogam. Most patients reported pain, itching, or local heat, 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 and no patient discontinued as a result of injection site reactions.

Reactions Associated with Immunoglobulins

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.

DOSAGE AND ADMINISTRATION

Evogam should only be administered **SUBCUTANEOUSLY**.

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

Dosage

The dose and dosage interval must be individualised for each patient based on their measured IgG trough levels and ongoing clinical response.

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).

Administration

Evogam is to be administered via the subcutaneous route, preferentially into the upper outer arms/upper thighs, abdomen, and/or lateral hip. **DO NOT ADMINISTER INTRAVENOUSLY.**

Evogam should be brought to room temperature before use.

The solution is clear and pale-yellow to light brown. If Evogam appears to be turbid or to contain sediment, it must not be used. The unopened bottle should be returned to the Australian Red Cross Blood Service. Evogam contains no antimicrobial preservative. Therefore it must be used immediately and administered within 4 hours of opening the bottle. Any unused portion should be discarded. Use in one patient on one occasion only. Do not use if the solution has been frozen.

A common Evogam weekly dose is 0.05-0.15 g (approximately 0.3-0.9 mL) per kg bodyweight, which may be administered at several infusion sites. When administering Evogam the recommended initial infusion rate is 10 mL/hour. The infusion rate may be gradually increased after the first completed infusion up to 20 mL/hour as comfort and tolerability allows. The maximum dose administered during clinical trials was 40 mL/hour using two infusion pumps simultaneously.

When large doses are given (> 20 mL), it is advisable to administer them in divided doses at different sites.

Subcutaneous infusion for home treatment

If the physician believes that home administration is appropriate, the physician or health professional should provide the patient with instructions on subcutaneous infusion for home treatment. This should include the use of subcutaneous administration techniques (including suitable infusion rates), how to maintain a treatment diary and measures to be taken in the case of severe adverse events.

OVERDOSAGE

Consequences of an overdose are not known.

PRESENTATION AND STORAGE CONDITIONS

The presentations available for Evogam are summarised in the table:

Amount of IgG (g)	Volume of solution (mL)	AUSTR
0.8	5	173315
1.6	10	173323
3.2	20	173324

Evogam is packaged in latex free materials. Store at 2°C to 8°C (Refrigerate. Do not freeze). Once removed from refrigeration, store below 25°C and use within 2 weeks. Protect from light.

Do not use after the expiry date.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4

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