Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nanogam 50 mg/ml
Solution for infusion
Human normal immunoglobulin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg) 50 g/l*
*corresponding to human protein content of which at least 95% is IgG.

One vial of 20 ml contains: 1 g of protein
One vial of 50 ml contains: 2.5 g of protein
One vial of 100 ml contains: 5 g of protein
One vial of 200 ml contains: 10 g of protein
One vial of 400 ml contains: 20 g of protein

Distribution of IgG subclasses:

IgG_1	54-70%
IgG_2	29-45%
IgG_3	1-4%
IgG_4	0-0.5%

IgA max. 6 microgram/ml

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The solution is clear or slightly opalescent, colourless or slightly yellowish.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
- Congenital AIDS with recurrent bacterial infections.

Immunomodulation in adults, and children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.

- Kawasaki disease.

4.2 Posology and method of administration

Posology

The dose and dose regimen is dependent on the indication.

REPLACEMENT THERAPY

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

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l. Three (3) to 6 months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4-0.8 g/kg given once, followed by at least 0.2 g/kg given every 3 to 4 weeks.

The dose required to achieve a trough level of 5-6 g/l is of the order of 0.2-0.8 g/kg/month. The dosage interval when steady state has been reached varies from 3-4 weeks.

Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels.

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections

The recommended dose is 0.2-0.4 g/kg every 3 to 4 weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation

The recommended dose is 0.2-0.4 g/kg every 3 to 4 weeks. The trough levels should be maintained above 5g/l.

IMMUNOMODULATION

Primary immune thrombocytopenia

There are 2 alternative treatment schedules:

- 0.8-1.0 g/kg given on day 1; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for 2 to 5 days.

The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day over 5 days.

Kawasaki Disease

1.6-2.0 g/kg should be administered in divided doses over 2 to 5 days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injections
Replacement therapy		
Primary immunodeficiency syndromes with impaired antibody production	- starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l
Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l
Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l
Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level above 5 g/l.
Congenital AIDS with recurrent bacterial infections.	0.2 - 0.4 g/kg	every 3 - 4 weeks
Immunomodulation		
Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.	0.8 - 1.0 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2 - 5 days
Guillain Barré syndrome	0.4 g/kg/d	for 5 days
Kawasaki disease	1.6 - 2.0 g/kg or 2.0 g/kg	in several doses for 2 - 5 days in association with acetylsalicylic acid in 1 dose in association with acetylsalicylic acid

Paediatric population

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

Method of administration

For intravenous use.

Human normal immunoglobulin should be infused intravenously at an initial rate of 0.5 ml/kg/hr for 20 minutes. If well tolerated (see section 4.4), the rate of administration may gradually be increased to 1.0 ml/kg/hr for 20 minutes and thereafter increased to a maximum of 3.0 ml/kg/hr for the first time users. In adult patients who receive Nanogam on a regular base with good tolerance, the infusion rate may be increased to a maximum of 7.0 ml/kg/hr.

For the administration of large quantities of Nanogam an Ethyl Vinyl Acetate-container may be used. See section 6.6.

4.3 Contraindications

Hypersensitivity to any of the components.
Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA.

4.4 Special warnings and precautions for use

This medicinal product contains 50 mg of glucose per ml as an excipient. This should be taken into account in case of latent diabetes (where transient glycosuria could appear), diabetes, or in patients on a low sugar diet. For acute renal failure see below.

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- 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 initially injecting the product slowly (0.01 ml/kg/min)
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

In case of an adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

In case of shock, standard medical treatment for shock should be implemented.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics.

<u>Hypersensitivity</u>

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

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.

<u>Thromboembolism</u>

There is clinical evidence of an association between IVIg administration and thromboembolic events such as

myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses 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 in prescribing and infusing IVIg 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, patients with diseases which increase blood viscosity).

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

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.

In case of renal impairment, IVIg 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. In patients at risk, the use of IVIg products that do not contain these excipients may be considered. Nanogam contains glucose (See excipients above). Nanogam does not contain sucrose or maltose.

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

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.

AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

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. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. (See section 4.8.)

Interference with serological testing

After injection of immunoglobulin 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 antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or

plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly after the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Lactation

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also Section 4.4).

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

Clinical studies

Two prospective uncontrolled multi-centre studies were performed to evaluate the safety and efficacy of Nanogam. In total, 42 patients have been exposed to the product in clinical trials which have received a total of 888 infusions.

The primary immunodeficiency (PID) study consisted of two parts. In the first part (short-term follow up / part A), 18 patients were included for a 6-month treatment. The patients received a dosage ranging from 150 to 400 mg/kg body weight every 2–5 weeks. All 18 patients (158 infusions) completed this part of the study. Subsequently, patients were asked to participate in part B, a long-term follow-up for efficacy and safety in which the same dosage regimen was used until Nanogam received marketing authorization (3 years after start of part B). Fourteen (14) out of 17 patients completed the study (669 infusions). Three (3) patients were withdrawn due to other reasons than AEs. One hypogammaglobulinemia patient experienced an allergic reaction (exanthema) similar to a previous allergic reaction which occurred while using other IVIg in the past. In total, 84 AEs were reported in the PID study, of which 43 (51.1 %) were drug related (39/158 infusions). The majority of these events were considered to be mild.

For the idiopathic thrombocytopenic purpura (ITP) study, 24 patients were included of which 8 patient received 1g/kg for 1 day, 9 patients received 1g/kg for two consecutive days, and 7 patients received 400 mg/kg for 5 consecutive days. Patients were followed up for a period of 14 days. Twenty-three (23) of 24 patients completed the study according to protocol. For 12 patients, a total of 31 AEs were reported of which 16 (51.6%) were possibly related to the product and were reported by 9 patients. In total, one or more side-effects, most mild to moderate, related to Nanogam, occurred in 10/61 infusions (16%).

In all patients, a decrease of haemoglobin has been observed while the liver- and haemoglobin levels were stable. The haemoglobin drop is considered to be probably a phenomenon of haemodilution and not caused by haemolysis due to Nanogam infusions.

The adverse drug reactions (ADRs) reported in the clinical trials of the patients are summarised and categorised according to the MedDRA system organ class in the table below. Frequencies have been evaluated according to the following convention:

- Very common (≥1/10);
- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);
- Rare (≥1/10,000 to <1/1,000);
- Very rare (<1/10,000)

Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

MedDRA (version 12) System Organ class (SOC)	**MedDRA preferred term**	**AR frequency**
Nervous System disorders	Headache	Common
	Dizziness	Uncommon

General disorders and administration site conditions	Malaise	Common
	Chills	Common
	Fatigue	Uncommon
	Sweating	Uncommon
	Flu-like symptoms	Uncommon
Investigations	Body temperature increased	Common
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
	Neck pain	Uncommon
	Myalgia	Uncommon
Gastrointestinal disorders	Diarrhoea	Uncommon
	Nausea*	Uncommon
Cardiac disorders	Tachycardia	Uncommon
Vascular disorders	Hypotension	Uncommon
Skin and subcutaneous tissue disorders	Exanthema*	Uncommon

* Reported single case in clinical studies
For safety with respect to transmissible agents, see 4.4.

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02
Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

5.2 Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient´s circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid,after approximately three to five days equilibrium is reached between the intra- and extravascular compartments .
Human normal immunoglobulin has a half-life of about 31 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

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

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body and hence conventional preclinical toxicity testing in animals is not feasible due to overloading of the circulation in acute toxicity testing and induction of antibodies in repeated dose studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Three years.

From a microbiological point of view, the product should be used immediately after puncturing of the rubber stopper. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless puncturing has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Within its shelf life, the product may be stored at or below 25°C for up to 6 months, without being refrigerated again. If not used during this period it must be discarded. The date when taken to room temperature should be marked on the package.

6.5 Nature and contents of container

20 ml of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
50 ml of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
100 ml of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
200 ml of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
400 ml of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.

To all of the above (5) presentations a pack size of 1 applies.
Not all presentations may be marketed

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

For patients receiving large quantities of Nanogam, it is also possible to transfer the contents of several vials to an Ethyl Vinyl Acetate container (Clintec® EVA-parenteral nutrition container, Baxter, CE0123). A maximum amount of 800 ml of Nanogam can be transferred to such a container. Use an aseptic technique for all the steps. For microbiological reasons, start the infusion as soon as possible after transfer of Nanogam into the EVA-container, but not later than three hours after the transfer.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sanquin
Plesmanlaan 125
NL-1066 CX Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1656/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th July 2011

10 DATE OF REVISION OF THE TEXT

March 2012