1. NAME OF THE MEDICINAL PRODUCT

Nanogam 100 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains 100 mg human normal immunoglobulin (purity of at least 95% IgG)

Each vial of 10 ml contains: 1 g of human normal immunoglobulin
Each vial of 25 ml contains: 2.5 g of human normal immunoglobulin
Each vial of 50 ml contains: 5 g of human normal immunoglobulin
Each vial of 100 ml contains: 10 g of human normal immunoglobulin
Each vial of 200 ml contains: 20 g of human normal immunoglobulin
Each vial of 300 ml contains: 30 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):

IgG_1 64.9%
IgG_2 31.8%
IgG_3 2.8%
IgG_4 0.5%

The maximum IgA content is 12 micrograms/ml.

Produced from the plasma of human donors.

Excipient(s) with known effect: glucose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

The solution is clear or slightly opalescent, colourless or pale yellow with an osmolality of 290-370 mosmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of < 4 g/l.

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

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 (in conjunction with acetylsalicylic acid; see 4.2).
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
- Multifocal motor neuropathy (MMN).

4.2 Posology and method of administration

Posology

The dose and dose regimen is dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.

The following dose regimens are given as a guideline.

REPLACEMENT THERAPY

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

Replacement therapy in primary immunodeficiency syndromes

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. Three to 6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) 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 IgG of 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 to 4 weeks.

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

Secondary immunodeficiencies (as defined in 4.1)

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

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

IMMUNOMODULATION

Primary immune thrombocytopenia

There are two alternative treatment schedules:

- 0.8-1 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 (possible repeat of dosing in case of relapse).

Kawasaki Disease

2 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Starting dose: 2 g/kg divided over 2 to 5 consecutive days
Maintenance doses:
1 g/kg over 1 to 2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal Motor Neuropathy (MMN)

Starting dose: 2 g/kg given over 2 to 5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of injections**
REPLACEMENT THERAPY		
Primary immunodeficiency syndromes	Starting dose: 0.4-0.8 g/kg Maintenance dose: 0.2-0.8 g/kg	 every 3-4 weeks
Secondary immunodeficiencies (as defined in 4.1)	0.2-0.4 g/kg	every 3-4 weeks
IMMUNOMODULATION		
Primary immune thrombocytopenia	0.8-1 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	2 g/kg	in 1 dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg	in divided doses over 2-5 days every 3 weeks over 1-2 days
Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg or 2 g/kg	over 2-5 consecutive days every 2-4 weeks or every 4-8 weeks over 2-5 days

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.

Hepatic impairment

No evidence is available to require a dose adjustment.

Renal impairment

No dose adjustment unless clinically warranted, see section 4.4.

Elderly

No dose adjustment unless clinically warranted, see section 4.4.

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, 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 of repeat infusions may be started at the last well-tolerated infusion rate or lower. If well tolerated, the rate of administration of regular Nanogam users may gradually be increased by 1.0 ml/kg/hr every 20 minutes up to a maximum of 7.0 ml/kg/hr. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.

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

Fluid balance, blood glucose and serum electrolytes may need to be monitored before and during administration (see sections 4.4, 4.5, 4.6 and 4.8).

4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients (see sections 4.4, 4.8 and 6.1). The excipient glucose is derived from corn.

Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

The solution is contraindicated in case of uncompensated diabetes, other known glucose intolerances (such as metabolic stress situation), hyperosmolar coma, hyperglycemia, and hyperlactataemia.

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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use

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 at the hospital 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 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 (see 4.5).

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.

Infusion reaction

Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) 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.

Adverse reactions may occur more frequently:

- 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.
- in patients with an untreated infection or underlying chronic inflammation

Hypersensitivity

Hypersensitivity reactions to the active substance (human immunoglobulins) or to any of the excipients (e.g. glucose) are rare.

Anaphylaxis can develop in patients

- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin.

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

Thromboembolism

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.

Renal parameters should be assessed prior to infusion of IVIG, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While 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.

Hyponatraemia

Depending on a patient's underlying clinical condition and capability to metabolize glucose, intravenous administration of glucose can cause electrolyte disturbances, most importantly hypo- or hyperosmotic hyponatraemia.

Patients with non-osmotic vasopressin release (e.g. in acute illness, pain, post-operative stress, infections, burns, central nervous system diseases), patients with heart, liver and kidney disease, and patients exposed to vasopressin agonists and other drugs that can lower serum sodium (see section 4.5) are at particular risk of acute hyponatraemia.

Acute hyponatraemia can lead to acute brain oedema and life-threatening, possibly irreversible, brain injury.

Children, women in the fertile age and patients with reduced cerebral compliance (e.g. meningitis, intracranial bleeding and cerebral contusion) are at particular risk of life-threatening brain swelling due to hyponatraemia. Rapid correction of hypoosmotic hyponatraemia is potentially dangerous (risk of serious neurologic complications).

Hyperglycemia

Administration of glucose containing solutions may produce hyperglycaemia and/or a hyperosmolar syndrome. Please take into consideration the following aspects:

• If hyperglycaemia occurs, rate of infusion should be adjusted and/or insulin administered.

• If necessary, provide parenteral supplements in potassium.

Intravenous solutions containing 5% glucose should be administered with caution in patients with impaired glucose tolerance (such as in diabetes mellitus, renal failure, or in the presence of sepsis, trauma, or shock), severe malnutrition, thiamine deficiency, e.g., in patients with chronic alcoholism (risk of severe lactic acidosis due to impaired oxidative metabolization of pyruvate), and ischemic stroke or severe traumatic brain injury.

Paediatric glycaemia-related issues

Newborns – especially those born premature and with low birth weight - are at increased risk of developing hypo- or hyperglycaemia and therefore need close monitoring during treatment with intravenous solutions that contains glucose to ensure adequate glycaemic control in order to avoid potential long term adverse effects.

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. 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 mm^3, 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.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

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).

Neutropenia/Leukopenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIgs. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing

After the administration 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 human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped viruses 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.

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.

Drugs that can increase the risk for hyponatraemia

Drugs that can lower serum sodium may increase the risk of acquired hyponatraemia following treatment with intravenous fluids inappropriately balanced to the need of the patient in terms of fluid volume and sodium content (see sections 4.4, 4.6 and 4.8). This concerns drugs that increase the vasopressin effect, such as chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, narcotics, NSAIDs, cyclophosphamide,

desmopressin, oxytocin, vasopressin and terlipressin. Other medicinal products increasing the risk of hyponatraemia also include diuretics and antiepileptics such as oxcarbazepine.

Loop diuretics

Avoidance of concomitant use of loop diuretics

Paediatric population

The listed interactions apply both to adults and children.

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 during 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 expected.

When Nanogam is administrated to pregnant women during labour, particularly if administered in combination with oxytocin, there may be an increased risk for hyponatraemia (see section 4.4, 4.5 and 4.8).

Breast-feeding

Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.

4.7 Effects on ability to drive and use machines

Nanogam has no or negligible influence on the 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 caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions, especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI).

Infusion of glucose containing intravenous fluids can cause hyponatraemia and hyponatraemic encephalopathy (see section 4.4). The frequency of occurrence of hyponatraemia and hyponatraemic encephalopathy is unknown.

Clinical studies

In the primary immunodeficiency (PID) study with Nanogam 50 mg/ml one hypogammaglobulinaemia patient experienced an allergic reaction (rash) 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 related to Nanogam 50 mg/ml. The majority of these events were considered to be mild.

In the primary immune thrombocytopenia (ITP) study, a total of 31 AEs for 12 patients were reported of which 16 (51.6%) were possibly related to Nanogam 50 mg/ml 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 in combination with stable liver functions and haptoglobin levels was observed. These cases were considered to be probably a phenomenon of haemodilution and not caused by haemolysis due to Nanogam infusions.

In the clinical trial performed with Nanogam 100 mg/ml in PID patients, 33 treatment-emergent AEs occurred in 16 patients (69.6%). There were no notable differences in the frequency and incidence per System Organ class (SOC) of the AEs between the Nanogam 50 mg/ml (period 1) and the Nanogam 100 mg/ml treatment (periods 2 to 5). Three of the 33 AEs were judged by the investigator to be possibly related to Nanogam 100 mg/ml. These AEs concerned three incidences of leukopenia ($< 4.0 * 10^9$/l) after infusion with Nanogam 100 mg/ml in two patients. The reported events of leukopenia were mild in intensity, and without clinical symptoms.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). 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); not known (cannot be estimated from the available data).

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

Frequency of Adverse Reactions (ADRs) obtained from post-marketing data with Nanogam.

MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency per patient**	**Frequency per infusion**
Blood and lymphatic system disorders	Leukopenia, neutropenia	Uncommon	Rare
Immune system disorders	Hypersensitivity reactions*	Common	Uncommon
Nervous system disorders	Migraine	Uncommon	Rare
	Headache	Common	Uncommon
	Dizziness	Uncommon	Rare
Cardiac disorders	Palpitations, Tachycardia	Uncommon	Rare
Vascular disorders	Hypertension, hypotension	Uncommon	Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon	Rare
Gastrointestinal disorders	Diarrhea	Uncommon	Rare
	Nausea	Common	Uncommon
Skin and subcutaneous tissue disorders	Skin disorders (rash, erythema, urticaria, pruritus, blister, exfoliation)	Common	Uncommon
	Hyperhidrosis	Uncommon	Rare
Musculoskeletal and connective tissue disorders	Back pain, neck pain, myalgia	Common	Uncommon

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency per patient	Frequency per infusion
General disorders and administration site conditions	Malaise (fatigue, chills, pyrexia, influenza like illness)	Common	Uncommon

* Potential manifestation in patients with allergy to active ingredients and/or excipients, see section 4.4.

For safety information with respect to transmissible agents, see section 4.4.

Paediatric population

Frequency, type and severity of adverse reactions in children are the same as in adults**.**

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via <the Dutch pharmacovigilance centre LAREB, Website www.lareb.nl >.

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment (see section 4.4). In case of suspected overdose, treatment with Nanogam must be stopped immediately.

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.

Clinical studies

Two prospective uncontrolled multi-centre studies were performed to evaluate the safety and efficacy of Nanogam 50 mg/ml. 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 to 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).

For the primary immune thrombocytopenia (ITP) study, 24 patients were included of which 8 patients received 1 g/kg for 1 day, 9 patients received 1 g/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 Nanogam 100 mg/ml one multicentre prospective uncontrolled clinical trial was performed. Aim of the study was to show bioequivalence between Nanogam 50 mg/ml and Nanogam 100 mg/ml. Twenty-three patients with primary immunodeficiency syndromes, who were already stabilised on treatment with Nanogam 50 mg/ml, were treated with one Nanogam 50 mg/ml infusion following their current treatment regimen and subsequently with four Nanogam 100 mg/ml infusions at the same dose interval and dose (in grams) as their regular treatment. The results of this study showed that the products are bioequivalent.

Paediatric population

There are no theoretical or observed differences in the action of immunoglobulins in children compared to adults.

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 3 to 5 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.

The pharmacokinetic profile of Nanogam after infusions is comparable using 50 mg/ml and 100 mg/ml strength, following the same infusion rate (ml/kg/hr).

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 given simultaneously with, before or after an administration of blood through the same infusion equipment, nor must it be mixed with other medicinal products or any other IVIg products.

6.3 Shelf life

3 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 in a refrigerator (2°C - 8°C). 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

10 ml (1 g) of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
25 ml (2.5 g) of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
50 ml (5 g) of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
100 ml (10 g) of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
200 ml (20 g) of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.
300 ml (30 g) of solution in a vial (Type II glass) with a stopper (bromobutyl) and a seal.

To all of the above 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 and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.

For patients receiving large quantities of Nanogam, it is also possible to transfer the contents of several vials to a single Ethyl Vinyl Acetate container (Clintec® EVA-parenteral nutrition container, Baxter, CE0123). These containers can be filled with Nanogam at a minimum of 20% up to a maximum of 80% of the total container volume for 500 ml and 1 L containers. 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 3 hours after the transfer.

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

7. MARKETING AUTHORISATION HOLDER

Prothya Biosolutions Netherlands B.V.
Plesmanlaan 125
NL-1066 CX Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

In the Netherlands: RVG118226

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

19 October 2021