VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Nanogam is intended to be used for the treatment of diseases in patients who are suffering from a shortage of immunoglobulins (antibodies) in their blood. Immunoglobulins are proteins with an important function in the natural defence system (immunological system) of individuals. A shortage of immunoglobulins gives cause to the immune system to malfunction.

Nanogam contains immunoglobulins and therefore, it can be used as replacement therapy in adults, and children and adolescents (0-18 years) in primary immunodeficiency syndromes with impaired antibody production. The most frequent primary immune deficiency syndromes are common variable immunodeficiency (CVID) and X-linked agammaglobulinaemia (XLA). Symptoms of CVID often manifest during childhood or adulthood. XLA is a X-chromosoom linked disease and therefore mainly males are affected. Symptoms of both CVID and XLA often are recurrent infections. These infections can be treated with intramuscular injections of immunoglobulins but that is very painful. An alternative option is to administer immunoglobulins intravenously.

Nanogam can also be used for the treatment of hypogammaglobulinaemia (shortage of immunoglobulins) and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL) , in whom prophylactic antibiotics have failed. CLL is a malignant disease of the white blood cells (lymphocytes). CLL is very uncommon under the age of 30 but its frequency of occurrence increases with age. Patients suffering from CLL often also suffer from infections. Those infections can be prevented and treated by the administration to the patient of immunoglobulins (Nanogam).

A third disease that can be treated with Nanogam is hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients. MM is a malignant disease also of the white blood cells but in this case it concerns the plasma cells. As CLL, MM is a disease of the elderly since the median age of diagnosis is 69 years. The causes of MM are poorly understood. Patients with MM frequently suffer from severe bacterial infections throughout the course of the disease. These infections can be prevented and treated by the administration of immunoglobulins (Nanogam).

Nanogam can also be used for the treatment of hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT). Patients receiving bone marrow from a donor for the treatment of mainly leukemic diseases often suffer from recurrent infections. These infections can be prevented and treated by the administration of immunoglobulins (Nanogam).

Finally, Nanogam can be used as replacement in children suffering from congenital AIDS with recurrent bacterial infections. AIDS is a disease of the immune system that causes the occurrence frequent infections. Those infections can be prevented and treated with Nanogam.

Besides replacement of immunoglobulins, another application of Nanogam is to use it to modulate the immune system. In some diseases (Primary immune thrombocytopenia, Guillain Barré syndrome, and Kawasaki disease), the immune system can be influenced (modulated) to help cure the disease.

Primary immune thrombocytopenia (ITP) is a disease that is characterised by a shortage of platelets (thrombocytes) in the blood. The dominant symptom of ITP is bleeding that becomes worse whit a greater shortage of platelets.

Guillain Barré syndrome (GBS) is an infectious disease of nerve cells. Symptoms consist of ascending paralysis, which is weakness beginning in the feet and hands and migrating to the trunk. Sometimes even the respiratory muscles can be affected which can cause life-threatening complications. Intravenous immunoglobolins (IVIG, Nanogam) is the preferred treatment option of GBS.

Kawasaki disease (KD) is thought to be inherited. It is most often observed in Japanese and Japanese-American children. Often KD begins with fever that is refractory to paracetamol. The most severe complication of KD is the development of abnormalities to the arteries of the heart (coronary artery dilatation). Early treatment with aspirin and intravenous immunoglobulins (IVIG, Nanogam) in most cases prevents the coronary artery dilatation from happening.

VI.2.2 Summary of treatment benefits

The indications for Nanogam are based on guidelines issued by the authorities (Core SPC for human normal immunoglobulin for intravenous administration (IVIG)" (CPMP/BPWG/859/95 rev. 1)). Two clinical trials have been performed: The first trial was performed to study the kinetics, efficacy and safety of Nanogam in hypogammaglobulinemia patients and the second trial was performed in adult patients with chronic idiopathic thrombocytopenic purpura (ITP) to investigate the safety and efficacy of Nanogam in ITP.

The first study was performed in 12 female and 6 male patients suffering from hypogammaglobulinemia. During the study for 12 patients, 25 infections have been reported. The majority of these were mild (65.5%) or moderate (30.4%). Six of the reported infections (13%) were severe, concerning sinusitis in 2 patients (both during 2 visits), an upper respiratory tract infection in one patient and an infection of the first digit of the left hand in another patient, respectively. Seven

patients had to stay absent from school or work due to infections, varying from 1 to 9 days per patient. Seven periods with fever have been reported for 5 patients. For 2 patients suffering a sinusitis, the number of days with fever was relatively large (20 days and 10 days, respectively). During this study 32 adverse events have been reported. Of these 17 were common or specific adverse events of which 16 were considered possibly related and 1 non-related. Other possibly related adverse events consisted of mild dizziness (1), moderate tiredness (1) and neck pain (1 mild, 4 moderate).

In the second study in 24 patients suffering from Thrombocytopenic Purpura (ITP), all patients showed an increase in platelet values after the infusion(s) with Nanogam. Though the majority of the patients could be defined as responders, in 3 patients the target value of at least 50x109/L was not reached. Therefore, in this study 83.3 % of the patients did have a response to treatment. Furthermore, at the end of the study 70.8% of the patients still had platelet values above baseline. During this study, 16 possibly related adverse events have been reported. Most reported side effects were headache and chills. In one patient, fever, chills and tachycardia (fast heart rate) was observed during the first infusion of Nanogam. This patient did not experience any adverse effect during the second infusion. In one patient, a drop of the haemoglobin level, possibly related to Nanogam infusion, was reported. However, the liver test functions remained stable during the infusion. Therefore it was concluded that the decrease of haemoglobin level was probably caused by haemodilution. One patient needed to be hospitalised for a planned splenectomy (removal of the spleen), but this was not considered to be related to Nanogam infusion.

VI.2.3 Unknowns relating to treatment benefits

For Nanogam no studies have been performed for specific groups such as pregnant or breastfeeding women, or patients with a poor liver of kidney function. However, since Nanogam contains immunoglobulins that are normally present in blood, there is no reason to assume that treatment of those patients would result in different effects or that it would give cause to other safety concerns than those currently identified. Nevertheless, Nanogam should be used in those individuals carefully.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Acute serious allergic reaction (anaphylactic or hypersensitivity reaction)	As for all products that are made from human blood there is a small chance that a patient would have a (severe) allergic reaction after the administration of Nanogam. Signs and symptoms of an allergic reaction are chest tightness, breathlessness and a low blood pressure. In scientific literature a case was reported on an	If a patient is known to have an allergy to one of the components of Nanogam, treatment should not be given. Patients with IgA-deficiency should use Nanogam with caution, due to a possible increased risk for allergic reactions or anaphylactic reactions.

Risk	What is known	Preventability
	assumed increased risk on allergic reactions in patients with IgA-deficiency[427].	
Blood clots (thromboembolic events)	The development of blood clots has been reported after treatment with Nanogam.	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.
Kidney failure (acute renal failure)	The development of kidney failure after treatment with Nanogam has been reported.	In patients at risk for kidney failure, IVIG products should be administered at the minimum rate of infusion and dose practicable.
Meningitis (Aseptic meningitis syndrome)	The development of meningitis after treatment with Nanogam has been reported.	When signs or symptoms of meningitis occur, IVIG treatment should be discontinued. Until now, this has resulted in remission of meningitis within several days.
Anaemia (Haemolytic anaemia)	The development of anaemia after treatment with Nanogam has been reported. Such anaemia is caused by the destruction of red blood cells (haemolysis).	Patients who are treated with an IVIG product should be monitored for clinical signs and symptoms of haemolysis.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Interfering with some specific laboratory tests (Interference with serological testing)	Treatment with Nanogam may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test.
Passing on infections (Transmission of infective 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 viruses such as HIV, HBV and HCV, and for 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.

Missing information

Risk	What is known
There is limited information on the use of Nanogam in pregnant or breast feeding women, patients with a poor kidney function, patients with a poor hepatic function, neonates and infants < 2years old, paediatric patients < 16 years old, and patients > 65 years old.	The safety of this medicinal product for use in human pregnancy has not been established in clinical studies. The immunoglobulins in Nanogam are natural constituents of human blood and function like normal immunoglobulins. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the new-born are to be expected. Also, clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected. Nevertheless, Nanogam should be used in to pregnant women and breast-feeding mothers cautiously and should be used only if clearly indicated. Patients with a poor kidney function: The immunoglobulins in

Risk	What is known
	Nanogam are natural constituents of human blood and function like normal immunoglobulins. Treatment with Nanogam is therefore not expected to be associated with any safety concern. Nevertheless, Nanogam should be used in those patients cautiously and should be used only if clearly indicated. Patients with a poor hepatic function: The immunoglobulins in Nanogam are natural constituents of human blood and function like normal immunoglobulins. Treatment with Nanogam is therefore not expected to be associated with any safety concern. Nevertheless, Nanogam should be used in those patients cautiously and should be used only if clearly indicated. Neonates and infants < 2years old: There is limited information on the use of Nanogam in this patient population. However, the immunoglobulins in Nanogam are natural constituents of human blood and function like normal immunoglobulins. Treatment with Nanogam is therefore not expected to be associated with any safety concern. Nevertheless, Nanogam should be used in those patients cautiously and should be used only if clearly indicated. Paediatric patients < 16 years old: There is limited information on the use of Nanogam in this patient population. However, the immunoglobulins in Nanogam are natural constituents of human blood and function like normal immunoglobulins. Treatment with Nanogam is therefore not expected to be associated with any safety concern. Nevertheless, Nanogam should be used in those patients cautiously and should be used only if clearly indicated. Patients > 65 years old: There is limited information on the use of Nanogam in this patient population. However, the immunoglobulins in Nanogam are natural constituents of human blood and function like normal immunoglobulins. Treatment with Nanogam is therefore not expected to be associated with any safety concern. Nevertheless, Nanogam should be used in those patients cautiously and should be used only if clearly indicated.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Nanogam can be made available on request. This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (planned, started)	Date for submission of interim or final reports
IUWP2005.01; EudraCT-no. 2006-005215-98.Phase IV efficacy study	Efficacy of Nanogam in patients with recurrent infections and IgG subclass deficiency, and/or deficient anti-polysaccharide antibody response, (subclass study)	Efficacy in this sub-population not yet established	Started	planned Q4 2014
MD2012.02; EudraCT-no. 2012-005727-32. Phase III pharmacokinetics study.	To establish pharmacokinetics and safety of the intravenous human immunoglobulin product Nanogam 100 mg/ml	The primary objective is to examine the pharmacokinetics of Nanogam 100 mg/ml and compare these with Nanogam 50 mg/ml. Aim is to show bioequivalency between Nanogam 50 mg/ml and Nanogam 100 mg/ml.	Started	planned March/April 2015
MD2009.01; EudraCT-number 2009-009463-61: Phase III efficacy study	Efficacy and safety of Nanogam in patients with idiopathic cardiomyopathy and endomyocardial	Efficacy and safety in this patient population not yet established	Started	Unknown

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (planned, started)	Date for submission of interim or final reports
	parvovirus B19 persistence.			
SID-GBS trail; EudraCT no. 2008-005659-83. Investigator Initiated Study	Efficacy of second IVIG Dose in GBS patients with poor prognosis, (SID-GBS trail)	Efficacy of second dose in patients with this disease state not yet established.	Started	Unknown
TIKI study; EudraCT number 2008-001597-33: Investigator Initiated Study	Development of chronic disease and safety of Nanogam in children newly diagnosed with ITP	Efficacy and safety in relation to disease development not yet established.	Started	Unknown
ALL11-IVIG; EudraCT number 2012-000067-25: Investigator Initiated Study	Efficacy and safety in children with newly diagnosed acute lymphoblastic leukaemia.	Efficacy and safety in children with ALL not yet established.	Started	Unknown

Studies which are a condition of the marketing authorisation

There are no studies which are a condition of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

This is the first Risk Management Plan.