ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vigam Liquid is a 5 % w/v normal immunoglobulin sterile liquid.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg) (IVIg)

One ml contains:
Human normal immunoglobulin 50 mg
(Purity of at least 95% IgG)

Each 2.5 g vial of 50 mL contains: 2.5 g of Human normal immunoglobulin.
Each 5 g vial of 100 mL contains: 5 g of Human normal immunoglobulin.
Each 10 g vial of 200 mL contains: 10 g of Human normal immunoglobulin.

Distribution of the IgG subclasses is similar to plasma (approximate values):
IgG1: 64 %
IgG2: 29 %
IgG3: 6 %
IgG4: 1 %

The maximum IgA content is 14 micrograms/ml.

Produced from the plasma of human donors.

Excipient(s):
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Vigam Liquid is a sterile liquid for intravenous administration which varies from colourless to pale amber or pale green.

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 and 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

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency. Treatment at home should be similarly supervised, with the patient fully assessed and trained in hospital prior to self-infusion at home.

Posology

The dose and dosage regimen is dependent on the indication.

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage 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 least5 to 6 g/L. Three to six 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 three to four 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; congenial AIDS with recurrent bacterial infections.

The recommended dose is 0.2 - 0.4 g/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation

The recommended dose is 0.2-0.4 g/kg every three to four weeks. The trough levels should be maintained above 5 g/L

Primary immune thrombocytopenia

There are two alternative treatment schedules:
- 0.8 - 1 g/kg on day one; this dose may be repeated once within 3 days,

- 0.4 g/kg given daily for two to five 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 two to five 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 in primary immunodeficiency	- 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
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg	Every 3 - 4 weeks to obtain IgG trough level of at least-5 - 6 g/L
Congenital AIDS	0.2 - 0.4 g/kg	Every 3 - 4 weeks
Hypogammaglobulinaemia (<4 g/L) in patients after allogeneic haematopoietic stem cell transplantation	0.2 - 0.4 g/kg	Every 3-4 weeks to obtain IgG trough level above 5g/L.
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	1.6 - 2 g/kg or	In divided doses over 2 - 5 days in association with acetylsalicylic acid
	2 g/kg	In one 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.

Vigam Liquid should be infused intravenously at an initial rate of 0.01 - 0.02 mL/kg/minute for 30 minutes. If well tolerated (see section 4.4), the rate of administration may be gradually increased to 0.04 mL/kg/minute up to a maximum of 3 mL/minute..

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.4)
Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

4.4 Special warnings and precautions for use

This medicinal product contains 2.4mg of sucrose per ml as an excipient. Reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, however those containing sucrose as an excipient accounted for a disproportionate share of the total number. 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 a 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 naïve 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 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 treatment 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 tolerated previous treatment with human normal immunoglobulin.

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 hypovolemic 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. Vigam Liquid contains sucrose

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 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 (2g/kg) IVIg treatment.

Haemolytic anaemia

IVIg products can obtain 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. The measures taken may be of limited value against non-enveloped viruses such as 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 Vigam Liquid 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.

Paediatric population

The listed warnings and precautions apply to both adults and children.

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.

Paediatric population

The listed interaction(s) apply to both adults and children

4.6 Fertility, pregnancy and lactation

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 to be expected.

Breast-feeding

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

Fertility

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

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 Vigam Liquid. 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.

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

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 reactions are presented in order of decreasing seriousness.

Frequency of Adverse Reactions (ADRs) in clinical studies with Vigam Liquid

MedDRA System Organ Class (SOC)	**Adverse Reaction**	**Frequency**
Nervous system disorders	Headache	Common
Vascular disorders	Hypertension NOS Hypotension NOS	Common Common
Respiratory, thoracic and mediastinal disorders	Pharyngitis	Common
Gastrointestinal disorders	Vomiting Nausea	Common Common
Skin and subcutaneous tissue disorders	Dermatitis exfoliative NOS Rash macular Urticaria NOS	Common Common Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Pyrexia Infusion site pain/inflammation Lethargy Fatigue	Very common Common Common Common

Description of selected adverse reactions

None of the reported adverse reactions to Vigam® Liquid warrant separate description

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults

Reporting of Suspected adverse reactions.

« If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly to the Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs
Fax: + 35722608649. By reporting side effects you can help provide more information on the safety of this medicine.»

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including older 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 immunoglobulins 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.

Paediatric population

There is no clinical data on the pharmacodynamics of Vigam Liquid in children.

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 - 5 days equilibrium is reached between intra- and extravascular compartments. Vigam Liquid has a half-life of about 23 - 25 days. This half life may vary from patient to patient, particularly in primary immunodeficiency.

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

Paediatric population

There is no clinical data on the pharmacokinetics of Vigam Liquid in children.

5.3 Preclinical safety data

Human proteins include antibodies in heterologous species. Therefore, pre-clinical studies have not been carried out with Vigam Liquid which contains immunoglobulins which are normal constituents of human blood.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human Albumin Solution 20% added at 2 g/100 mL
Sodium n-octanoate
Sucrose
Sodium acetate
Glycine

6.2 Incompatibilities

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

6.3 Shelf life

24 months if stored unopened between 2ºC and 8ºC.

6.4 Special precautions for storage

Vigam Liquid should be stored in its carton to protect it from light, between 2° and 8°C.

DO NOT FREEZE.

A short period up to 3 months at 25°C is possible within the shelf-life period**.**

Do not use after the expiry date printed on the label. The conditions of expired or incorrectly stored product cannot be guaranteed. Such product may be unsafe and should not be used.

6.5 Nature and contents of container

Vigam Liquid is a sterile colourless to pale amber or pale green liquid immunoglobulin G supplied as 2.5 g, 5 g and 10 g doses. The product is contained in a clear glass bottle and stoppered with a rubber bung. The bung is over-sealed with a tamper-evident cap.

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.

Use of Vigam Liquid should begin immediately after piercing the cap.
Vigam Liquid is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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