MODULE 1.3 SOUTH AFRICAN LABELLING AND PACKAGING

1.3.1 South African Package Insert

1.3.1.1 Proposed Package Insert

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

Polygam ® 1 g Lyophilised powder for IV infusion

Polygam ® 3 g Lyophilised powder for IV infusion

Polygam ® 6 g Lyophilised powder for IV infusion

Polygam ® 12 g Lyophilised powder for IV infusion

COMPOSITION

Descriptive name: Polyvalent human normal immunoglobulin.

Polygam 1 g

1 g polyvalent human normal immunoglobulin per 50 ml (2 % solution) after reconstitution with sodium chloride 0,9 % *m/v*.

Inactive ingredient: Contains sugar, Sucrose: ≥ 1,40 g (stabiliser)

Polygam 3 g

3 g polyvalent human normal immunoglobulin per 100 ml (3 % solution) after reconstitution with sodium chloride 0,9 % *m/v.*

Inactive ingredient: Contains sugar, Sucrose: ≥ 4,20 g (stabiliser)

Polygam 6 g

6 g polyvalent human normal immunoglobulin per 200 ml (3 % solution) after reconstitution with sodium chloride 0,9 % *m/v*.

Inactive ingredient: Contains sugar, Sucrose: ≥ 8,40 g (stabiliser)

Polygam 12 g

12 g polyvalent human normal immunoglobulin per 400 ml (3 % solution)

after reconstitution with sodium chloride 0,9 % *m/v*.

Inactive ingredient: Contains sugar, Sucrose: ≥ 16,80 g (stabiliser)

Polygam contains no antimicrobial preservative.

Polygam includes a normal distribution of IgG subclasses derived from pooled human plasma from not less than 1000 healthy, volunteer, non-remunerated donors.

Polygam consists primarily of monomeric immunoglobulin G (IgG) and contains trace amounts of IgA and IgM.

Each unit of plasma has been individually tested and found non-reactive for hepatitis B surface antigen (HBsAg), antibodies to the hepatitis C virus (HCV) and antibodies to the human immunodeficiency viruses, HIV-1 and HIV-2, using approved methods.

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, testing of plasma pools by NAT (Nucleic Acid Amplification Technology) for HCV, HIV, HAV (hepatitis A virus) and

HBV (hepatitis B virus), and the inclusion of effective manufacturing steps for the inactivation/removal of viruses.

Polygam is prepared by cold ethanol fractionation and pH 4,0 pepsin treatment to further reduce the risk of viral transmission. The pH 4,0 pepsin process has been validated and shown to be effective against enveloped viruses HIV, HBV and HCV.

PHARMACOLOGICAL CLASSIFICATION

A 30.2 Biologicals (Antibodies).

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Polyvalent human normal immunoglobulin confers passive immunity.

Polyvalent human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. The preparation contains all the immunoglobulin and subclass activities that are present in the normal population. Adequate doses of this 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.

Pharmacokinetic properties

Polyvalent human normal immunoglobulin is immediately and completely bioavailable in the patient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, and after approximately 3 - 5 days equilibrium is reached between the intra- and extravascular compartments.

Polyvalent human normal immunoglobulin has a half-life of about 19 - 27 days in normal individuals. This half-life may vary from patient to patient and is also dependent on the

patient's diagnosis. It is therefore recommended that the half-life be used as a guideline only and that the patient is appropriately monitored for adequate clinical response. (See "**DOSAGE AND DIRECTIONS FOR USE**".)

INDICATIONS

Replacement therapy in primary antibody deficiency syndromes.

Myeloma or chronic lymphocytic leukaemia with severe hypogammaglobulinaemia and recurrent infections.

Children with congenital AIDS and recurrent infections.

For immunomodulation in:

* Idiopathic Thrombocytopenic Purpura (ITP) in children and adults.
* Kawasaki disease.
* Guillain Barré Syndrome.

Allogeneic bone marrow transplantation.

CONTRA-INDICATIONS

Where there is known hypersensitivity, the risk of hypersensitive reactions should be weighed against that of the disease.

Polygam should be given with caution to patients with antibodies to IgA or selective IgA deficiencies as the small amounts of IgA present in **Polygam** may cause sensitisation. Sensitisation could lead to a severe allergic reaction, anaphylaxis in patients with antibodies to IgA, or subsequent reaction to other IgA-containing material (including human blood and plasma-derived medicinal products).

WARNINGS AND SPECIAL PRECAUTIONS

Measures to treat anaphylaxis, including adrenaline and corticosteroids, must be at hand when administering **Polygam.**

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.

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.

Volume may be a problem in patients with limited cardiac function especially with higher doses

Caution should be exercised in the administration of **Polygam** in patients at increased risk for developing acute renal failure. Such patients include, but are not limited to, those with:

- any degree of pre-existing renal insufficiency
- diabetes mellitus
- age greater than 65 years
- volume depletion
- sepsis, paraproteinaemia
- concomitant nephrotoxic drugs
- overweight patients

For patients at increased risk, the potential benefits should be weighed against the risks of

causing renal damage.

The risk for developing acute renal failure can be minimised by:

- ensuring adequate hydration prior to the initiation of therapy,
- avoidance of concomitant use of loop diuretics,
- monitoring of urine output and serum creatinine prior to infusion of therapy and then again at appropriate intervals. Should the renal function deteriorate, consideration should be given to the discontinuation of the product,
- reduction in dose, concentration and/or rate of administration in patients at risk of acute renal failure are also recommended.

There is clinical evidence of a possible association between intravenous immunoglobulin administration and thrombotic events. The exact cause is unknown; therefore, caution should be exercised in the prescribing and infusion of IVIG in patients with a history of cardiovascular disease or thrombotic episodes.

Polygam contains sucrose as a stabiliser. As sucrose is excreted unchanged in the urine after IV administration, no precautionary measures need to be taken in diabetic patients who require medication to control their blood sugar levels.

INTERACTIONS

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 the 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 should have their antibody status checked.

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 transfusion of antibodies to erythrocyte antigens e.g. A,B,D may interfere with some serological tests for red cell allo-antibodies.

PREGNANCY AND LACTATION

The safety of polyvalent human normal immunoglobulin for use in human pregnancy has not been established in controlled clinical trials and **Polygam** should therefore only be given with caution to pregnant women and breastfeeding mothers. 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.

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

DOSAGE AND DIRECTIONS FOR USE

Dosage

The dose and dosage regimen is dependent on the indication and the *in vivo* half-life of the IgG molecules in the individual patient. The following intravenous dosage regimens are given as a guideline only:

Replacement Therapy in Immunodeficiency:		
Indication:	**Dose:**	**Frequency of Infusions:**
Primary immunodeficiency:	Starting dose: 0,4 – 0,8 g/kg thereafter: 0,2 – 0,8 g/kg	every 2 - 4 weeks to obtain IgG trough levels of at least 4 - 6 g/L
Secondary immunodeficiency:	0,2 – 0,4 g/kg	every 3 - 4 weeks to obtain IgG trough levels of at least 4 - 6 g/L
Children with AIDS:	0,2 – 0,4 g/kg	every 3 - 4 weeks

Immunomodulation:		
Indication:	**Dose:**	**Frequency of Infusions:**
Idiopathic Thrombocytopenic Purpura:	0,8 – 1 g/kg or 0,4 g/kg/day	on day 1, may be repeated once within 3 days or for 2 - 5 days. May be repeated if relapse occurs

Kawasaki Disease:	2 g/kg or 1,6 – 2 g/kg	as a single dose in conjunction with aspirin or in divided doses for 2 - 5 days in conjunction with aspirin
Guillain Barré Syndrome:	0,4 g/kg/day	for 3 - 7 days
Allogeneic bone marrow transplantation:		
Indication:	**Dose:**	**Frequency of Infusions:**
Treatment of infections and prophylaxis of graft versus host disease:	Starting dose: 0,5 g/kg	every week starting 7 days before transplantation and up to 3 months after transplantation
Persistent lack of antibody production:	0,5 g/kg	every month until antibody levels return to normal

Polygam 1 g is administered as a 2 % solution. **Polygam 3 g, 6 g, 12 g** may be administered as a 3 % or 6 % solution. The first infusion of **Polygam 3 g, 6 g, 12 g** must be administered as a 3 % solution. Should the patient's condition necessitate a reduced volume of infusion, the second and further infusions may then be administered as a 6 % solution. (See "**WARNINGS AND SPECIAL PRECAUTIONS**").

Reconstitution procedures:

Please note: Polygam 1 g is supplied with one diluent bag for reconstitution to a 2

% solution. Polygam 3 g, 6 g and 12 g are supplied with two diluent bags. To reconstitute to a 3 % solution, both diluent bags must be used and for a 6 % solution only one diluent bag is required.

1. Remove the closure from the **Polygam** bottle and swab the exposed rubber stopper with a suitable antibacterial agent.

2. Clamp the transfer set and insert the plastic connector into the outlet port of the diluent bag and the needle into the port on the rubber stopper of the **Polygam** bottle.

3. Raise the diluent above the **Polygam** bottle, release the clamp and the vacuum will draw the diluent into the bottle.

   Do not use the product if no vacuum is present.

   Please note: **Polygam** is packed under vacuum. If this vacuum is lost during reconstitution, it may be difficult to reconstitute this product as the diluent flow into the bottle will decrease and eventually stop. Should this occur, insert an airvent needle through the rubber stopper and draw the diluent into the bottle by gravity.

4.1 **For a 6 % solution:**

Once the transfer of the diluent is complete, remove and discard the transfer set and diluent bag.

4.2 **For a 3 % solution:**

Once the transfer of the first diluent is complete, re-clamp the transfer set, remove and discard the diluent bag whilst the transfer set remains inserted in the port. Attach the second diluent bag to the transfer set, release the clamp and again the vacuum will draw the diluent into the bottle. Once the transfer of the diluent is complete, remove and discard the transfer set and diluent bag.

5. Gently swirl the bottle. **Do not shake and avoid foaming of the solution**. Insert

the airvent needle approximately 2 mm from the port on the rubber stopper to break the vacuum. Allow the product to stand, swirling occasionally, until completely dissolved. This may take up to 30 minutes.

Intravenous administration

Please note: The reconstituted solution is slightly opalescent.

Do not use if the solution is turbid or discoloured.

Do not combine with other intravenous preparations.

Infuse immediately after reconstitution.

Infuse the product through an appropriate administration set with an in-line filter, inserted into the port on the rubber stopper of the bottle, with the airvent needle in place to vent the infusion.

It is strongly recommended that every time Polygam is administered to the 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.

Infusion rate

The infusion rate recommended is calculated using a 20 drop per ml administration set.

The infusion should be commenced at a rate of 10 to 20 drops per minute (30 – 60 ml/hour), increasing to 20 to 30 drops per minute (60 – 90 ml/hour) after 15 minutes. The flow rate may be increased to a maximum flow rate of 40 to 50 drops per minute (120 - 150 ml/hour) if well tolerated by the patient.

Close adherence to the recommended infusion rate is required to prevent adverse reactions. If the rate of infusion is kept low, the risk of side effects is lessened. Should adverse reactions occur, the administration rate must be decreased or the infusion

stopped until the symptoms disappear.

In certain patient groups it is advisable to determine the maximum safe rate of infusion based on the body mass of the patient.

The following administration rate is recommended: 0,01 - 0,02 ml/kg/min for the first 30 minutes, then gradually increased to a maximum of 0,08 ml/kg/min for the remainder of the infusion.

Discard any unused product.

SIDE EFFECTS

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.

The following side effects may occur:

Skin and Appendages disorders:

Common: Rash

Uncommon: Erythema, urticaria and transient cutaneous reactions

Musculo-Skeletal System disorders: Uncommon: Joint pain,

myalgia

Central and Peripheral Nervous System disorders:

Common: Faintness

Uncommon: Reversible aseptic meningitis syndrome (AMS) has been reported. The syndrome usually begins within several hours to 2 days following IVIG (intravenous immunoglobulin) therapy. Patients with a history of migraine or those treated with higher doses of IVIG seem to be at higher risk.

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

Rare: Burning sensation in the head, leg cramps

Gastro-Intestinal disorders: Uncommon: Nausea and vomiting

Cardiovascular disorders, general: Common: Hypotension

Heart Rate and Rhythm disorders: Uncommon: Tachycardia

Respiratory System disorders: Common: Dyspnoea, wheezing

Platelet, Bleeding and Clotting disorders:

Very Rare: Thrombotic events have been reported in the elderly, in patients with signs of cerebral or cardiac ischaemia and in overweight and severely hypovolaemic patients.

Cases of reversible haemolytic anaemia/haemolysis have also been reported.

Urinary System disorders:

Uncommon: Increase in serum creatinine level and/or acute renal failure have been reported (see "**WARNINGS AND SPECIAL PRECAUTIONS**").

Body as a Whole/General Disorders:

Common: Fever, headache

Rare: Backache, malaise, fatigue, chest pain, allergic reactions, chills A fall in blood pressure and anaphylactic reactions may occur, particularly in patients with IgA deficiency who may produce antibodies to IgA. These reactions generally become evident within 30 to 60 minutes after administration. Patients with agammaglobulinaemia or severe hypogammaglobulinaemia who are receiving intravenous immunoglobulin therapy for the

First time may be at increased risk of developing inflammatory reactions, which may lead to shock, especially if administered by rapid infusion. (Refer to "**WARNINGS AND SPECIAL PRECAUTIONS**") It appears that most side effects are related to the rate of infusion, and may be relieved by decreasing the rate or temporarily stopping the infusion.

Application Site disorders: Uncommon: Pain at the injection site

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENT

See "**SIDE EFFECTS**". Treatment is symptomatic and supportive.

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

IDENTIFICATION

Lyophilised powder: a white, amorphous powder.

Reconstituted solution: slightly opalescent solution.

PRESENTATION

Each pack consists of a clear glass bottle containing lyophilised immunoglobulin powder, bag(s) of 0,9 % *m/v* sodium chloride diluent and a reconstitution set.

The following pack sizes are available:

1 g immunoglobulin with 1 x 50 ml normal saline bag

3 g immunoglobulin with 2 x 50 ml normal saline bags

6 g immunoglobulin with 2 x 100 ml normal saline bags

12 g immunoglobulin with 2 x 200 ml normal saline bags

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light.

Keep out of reach of children.

REGISTRATION NUMBERS

Polygam® 1 g: Z/30.2/367

Polygam® 3 g: Z/30.2/368

Polygam® 6 g: Z/30.2/369

Polygam® 12 g: 29/30.2/511

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

NATIONAL BIOPRODUCTS INSTITUTE NPC

Company Reg. No. 1994/002044/08

NPO Reg. No. 020-898-NPO

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

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NAMIBIA S2

Reg. No.:

Polygam® 1g: 04/30.2/1040

Polygam® 3g: 04/30.2/1041

Polygam® 6g: 04/30.2/1042

Polygam® 12g: 04/30.2/1045