PATIENT INFORMATION LEAFLET

WARNING:

THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including PRIVIGEN. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of oestrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients.**

SCHEDULING STATUS: S4

PRIVIGEN 25 ml solution for infusion for intravenous use.

PRIVIGEN 50 ml solution for infusion for intravenous use.

PRIVIGEN 100 ml solution for infusion for intravenous use.

Human normal immunoglobulin.

Sugar free.

Read all of this leaflet carefully before you start using PRIVIGEN

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.

WHAT IS IN THIS LEAFLET

1. WHAT PRIVIGEN IS AND WHAT IT IS USED FOR

PRIVIGEN belongs to the class of medicines called human normal immunoglobulins. Immunoglobulins are also known as antibodies and are blood proteins that help your body to fight infections.
PRIVIGEN contains immunoglobulins that have been prepared from the blood of healthy people. The medicine works in exactly the same way as the immunoglobulins naturally present in human blood of healthy people.

PRIVIGEN is used for the treatment of adults and children (0-18 years) in the following situations:

a) <u>to increase abnormally low immunoglobulin levels in your blood to normal levels (replacement therapy):</u>

1. Patients who are born with a reduced ability or inability to produce immunoglobulins (primary immunodeficiencies (PID)).
2. Patients with an acquired immunodeficiency (SID) who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of < 4 g/L.

b) <u>to treat certain inflammatory disorders (immunomodulation). There are 5 groups:</u>

1. Patients who do not have enough blood platelets (primary immune thrombocytopenia (ITP) and who are at high risk of bleeding or will have surgery in the near future.
2. Patients with Guillain-Barré syndrome. This is an acute disease that is characterised by inflammation of the peripheral nerves that causes severe muscle weakness mainly in the legs and upper limbs.
3. Patients with Kawasaki disease. This is an acute disease that primarily affects young children. It is characterised by inflammation of blood vessels throughout the body.

4. Patients with chronic inflammatory demyelinating polyneuropathy (CIDP). This is a chronic disease that is characterised by inflammation of the peripheral nerves that causes muscle weakness and/or numbness mainly in the legs and upper limbs.
5. Patients with multifocal motor neuropathy (MMN). This is a slowly progressive disease of the motor nerves with weakness of arms and legs.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN PRIVIGEN

PRIVIGEN should not be administered to you:

- if you are allergic to human immunoglobulins or to proline.
- if you have developed antibodies against immunoglobulins of the type IgA in your blood.
- if you suffer from hyperprolinaemia type I or II (a genetic disorder causing high levels of the amino acid proline in the blood). This is an extremely rare disorder. Only a few families with this disease are known worldwide.

Warnings and precautions:

Tell your doctor or healthcare professional prior to treatment if any of the circumstances listed below applies to you:

- You receive this medicine in high doses either on 1 day or over several days and you have a blood group A, B or AB and/or you have an underlying inflammatory condition. In these circumstances, it has been commonly reported that immunoglobulins increase the risk of breakdown of red blood cells (haemolysis).
- You are overweight, are elderly, have diabetes, have been bedridden for a long time, have high blood pressure, have low blood volume (hypovolaemia), have problems with your blood vessels (vascular diseases), have an increased tendency for blood clotting (thrombophilia or thrombotic episodes) or have a disease or a condition which causes your blood to thicken (hyperviscous blood). In these circumstances, immunoglobulins may increase the risk of heart attack (cardiac infarction), stroke, blood clots in the lung (lung embolism), or blockage of a blood vessel in the leg, although only very rarely.

- You are diabetic. Although PRIVIGEN does not contain sugar, it may be diluted with a special sugar solution (5 % glucose), which could affect your blood sugar level.
- You have or had previously problems with your kidneys or take medicinal products that may harm your kidneys (nephrotoxic medicinal products). In these circumstances, immunoglobulins may increase the risk of serious rapid loss of kidney function (acute renal failure) although only very rarely. Loss of kidney function with fatal outcome has occurred in isolated haemolysis-related cases.

What kind of monitoring is required during the infusion?

For your personal safety, treatment with PRIVIGEN will take place under the supervision of your doctor or healthcare professional. You will usually be observed during the whole infusion and for at least 20 minutes thereafter. In certain circumstances, special precautions may be necessary. Examples of such circumstances are:

- you are receiving PRIVIGEN at a high infusion rate *or*
- you are receiving PRIVIGEN for the first time or after a long break in treatment (e.g. several months).

In these cases you will be closely observed during the whole infusion and for at least 1 hour afterwards.

When may slowing or stopping the infusion be required?

- You may be allergic (hypersensitive) to immunoglobulins without knowing it.
  However, true allergic reactions are rare. They may occur even if you have previously received human immunoglobulins and had tolerated them well. It may happen particularly if you have developed antibodies against immunoglobulins of the type IgA. In these rare cases allergic reactions such as a sudden fall in blood pressure or shock may occur (see also section 4 "Possible side effects").
- In very rare cases transfusion-related acute lung injury (TRALI) can occur after receiving immunoglobulins. This will lead to non-heart related accumulation of fluid in the air spaces of the lungs (non-cardiogenic pulmonary oedema). You will recognize TRALI by severe difficulty in

breathing (respiratory distress), abnormally low level of oxygen in the blood (hypoxemia), normal heart function (left ventricular function) and increased body temperature (fever). Symptoms typically appear within 1 to 6 hours after receiving treatment.

Tell your doctor or healthcare professional immediately if you notice such reactions during the infusion of PRIVIGEN. He or she will decide whether to decrease the infusion rate or to stop the infusion completely.

Blood tests:

- Tell your doctor about your treatment with PRIVIGEN prior to having any blood tests.

After receiving PRIVIGEN, the results of certain blood tests (serological tests) may be impaired for a certain time.

Information on safety with respect to infections:

PRIVIGEN is made from human blood plasma (this is the liquid part of the blood).

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses and other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus and parvovirus B19.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections, possibly because antibodies against these infections, which are contained in the product, are protective.

- It is strongly recommended that every time you are given a dose of PRIVIGEN the name and batch number of the product are recorded in order to maintain a record of the batches used.

Other medicines and PRIVIGEN:

Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)

Vaccinations:

- Tell your vaccinating doctor prior to a vaccination about your treatment with PRIVIGEN.

After receiving PRIVIGEN, the efficacy of certain vaccinations may be impaired. Affected are vaccinations with live attenuated virus vaccines such as vaccinations against measles, mumps, rubella and varicella. Such vaccinations should be postponed for at least 3 months after the last infusion of PRIVIGEN. In the case of measles vaccinations the impairment may persist for up to 1 year. Therefore, your vaccinating doctor should check the effectiveness of the measles vaccination.

Pregnancy, breastfeeding and fertility:

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before receiving this medicine.
Your doctor will decide whether you can receive PRIVIGEN during your pregnancy or while you are breast-feeding.
Medicines containing antibodies have been used in pregnant and breast-feeding women. Long-term experience has shown that no harmful effects during the course of the pregnancy or to the newborn are to be expected.
If you receive PRIVIGEN while you are breast-feeding the antibodies in this medicine will also be found in the breast milk. Thus, also your baby can receive the protective antibodies.

Driving and using machines:

Patients may experience effects, such as dizziness or nausea, during treatment with PRIVIGEN that might affect the ability to drive and use machines. If this happens, you should not drive or use machines until these effects have disappeared.

PRIVIGEN contains proline:

You must not take PRIVIGEN if you suffer from hyperprolinaemia (see also section 2 "What you need to know before you are given PRIVIGEN"). Tell your doctor prior to treatment if you suffer from hyperprolinaemia.

3. HOW TO USE PRIVIGEN

PRIVIGEN is intended solely for the infusion into a vein (intravenous infusion).
You will not be expected to give yourself PRIVIGEN. It will be given to you by a person who is qualified to do so.
Your doctor will calculate the correct dose for you taking into account your weight, the specific circumstances listed under section 2 "Warnings and precautions" and response to treatment. The dose calculation for children and young patients is not different from that for adults. At the beginning of the infusion you will receive PRIVIGEN at a slow infusion rate. If you tolerate this well, your doctor can gradually increase the infusion rate.

If you have the impression that the effect of PRIVIGEN is too strong or too weak, tell your doctor or pharmacist.

If you take more PRIVIGEN than you should:

Overdose is very unlikely to occur because PRIVIGEN is usually administered under medical supervision.
Since a health care provider will administer PRIVIGEN, he / she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you receive more PRIVIGEN than you should, your blood may become too thick (hyperviscous) which might increase the risk of developing blood clots. This may happen particularly if you are a patient at risk, for example if you are elderly or if you suffer from a heart or kidney disease. Tell your doctor if you are known to have medical problems.

If you forget to take PRIVIGEN:

Since a health care provider will administer PRIVIGEN, it is unlikely that the dose will be missed.

4. Possible side effects:

PRIVIGEN can have side effects.

Possible side effects may be reduced or even avoided by infusing PRIVIGEN at a slow infusion rate.

Such side effects may occur even if you have previously received human immunoglobulins and tolerated them well.

Not all side effects reported for PRIVIGEN are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking PRIVIGEN, please consult your healthcare provider for advice.

In rare and isolated cases, the following side effects have been reported with immunoglobulin preparations:

- severe hypersensitivity reactions such as a sudden fall in blood pressure or anaphylactic shock (e.g. you may feel light-headed, dizzy, faint on standing, cold in the hands and feet, sense an abnormal heart beat or chest pain, or have blurred vision) even when you have shown no hypersensitivity on previous infusions,

  Tell your doctor or healthcare professional immediately if you notice such signs during the infusion of PRIVIGEN. He or she will decide whether to decrease the infusion rate or to stop the infusion completely.

- formation of blood clots which may be carried off in the blood circulation (thromboembolic reactions) and which may result e.g. in myocardial infarction (e.g. when you have sudden chest pain or shortness of breath), stroke (e.g. when you have a sudden onset of muscle weakness, have loss of sensation and/or balance, decreased alertness or difficulty in speaking), blood clots in the arteries of the lungs (e.g. when you have chest pain, difficulty in breathing or are coughing up blood), deep vein thrombosis (e.g. when you have redness, feel warmth, pain, tenderness, or have a swelling of one or both legs),
- chest pain, chest discomfort, painful respiration due to transfusion related lung injury (TRALI).

Tell your doctor or healthcare professional immediately if you have any of the above symptoms. Anyone experiencing such symptoms should immediately be transported to to the casualty department at the nearest hospital for evaluation and treatment.

- temporary non-infectious meningitis (reversible aseptic meningitis)

Tell your doctor or healthcare professional immediately if you have a stiff neck together with one or more of the following symptoms: fever, nausea, vomiting, headache, abnormal sensitivity to light, mental disturbances.

- increase in blood creatinine level,
- proteinuria,
- acute renal failure,
- transient decrease in red blood cells (reversible haemolytic anaemia/haemolysis), anaemia, leukopenia, anisocytosis (including microcytosis).

Side effects observed in controlled clinical studies and in post-marketing experience are presented in order of decreasing frequency:

Very Common (may occur with more than 1 in 10 patients):

Headache (including sinus headache, migraine, head discomfort, tension headache), upset stomach (nausea), pain (including back pain, pain in extremity, pain in joints and bones (arthralgia), neck pain, facial pain), fever (including chills), flu-like illness (including runny nose (nasopharyngitis), sore throat (pharyngolaryngeal pain), blisters in mouth and throat (oropharyngeal blistering), throat tightness.

Common (may occur with up to 1 in 10 patients):

Temporary lowering of red blood cell count (anaemia), breakdown of red blood cells (haemolysis), decreased number of white blood cells (leukopenia), hypersensitivity, dizziness (including vertigo), high blood pressure (hypertension), flushing (including hot flush, hyperaemia), hypotension (including decreased blood pressure), breathlessness (dyspnoea including chest pain, chest discomfort, painful breathing), vomiting, loose stools (diarrhoea), stomach pain, skin disorder (including rash, itching (pruritus), hives (urticaria), maculopapular rash, redness of the skin (erythema), peeling of the skin (skin exfoliation)), pain in the muscles (including muscle cramps and rigidity), tiredness (fatigue), physical weakness (asthenia), weakness in the muscles, .

Routine laboratory tests may commonly reveal changes to liver functions (hyperbilirubinaemia) as well as changes in blood count (e.g. Coombs' (direct) test positive), increased alanine aminotransferase, increased aspartate aminotransferase, increased blood lactate dehydrogenase).

Uncommon (may occur with up to 1 in 100 patients):

Temporary non-infectious meningitis (reversible aseptic meningitis), irregularity of red blood cell shape (microscopic finding), presence of high platelet counts in the blood (thrombocytosis), sleepiness, shiver (tremor), palpitations, tachycardia, thromboembolic events, lack of blood supply to the lower extremities causing e.g. pain when walking (peripheral vascular disorder), presence of an excess of serum proteins in the urine (proteinuria including increased blood creatinine), injection site pain.

In isolated cases (post-marketing experience), the following have been observed in patients treated with PRIVIGEN: abnormally low level of specific white blood cells called neutrophils (decreased neutrophils counts), anaphylactic shock, painful respiration due to transfusion related lung injury (TRALI) and acute renal failure.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects:

If you get side effects, talk to your doctor, pharmacist or healthcare professional. This includes any possible side effects not listed in this leaflet. You can report side effects to Gen-Eye (Pty) Ltd via email: pharmacovigilance@geneye.co.za or telephonically on 011 312 3812. You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of PRIVIGEN.

5. HOW TO STORE PRIVIGEN

Store all medicines out of reach of children.

Do not store above 25 °C.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Because the solution contains no preservative, your healthcare professional must infuse it immediately after opening the vial.

Do not use this medicine if you notice that the solution is cloudy or contains particles floating within the solution.

Do not use after the expiry date stated on the carton and vial.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What PRIVIGEN contains:

The active substance is human normal immunoglobulin.

Each ml contains:

Human normal immunoglobulin 100 mg

(purity of at least 98 % IgG)

Each vial of 25 ml solution contains: 2,5 g human normal immunoglobulin

Each vial of 50 ml solution contains: 5 g human normal immunoglobulin

Each vial of 100 ml solution contains: 10 g human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):

IgG_1 ..... 69 %

IgG_2 ..... 26 %

IgG_3 ..... 3 %

IgG_4 ..... 2 %

The maximum IgA content is 25 micrograms/mL PRIVIGEN is essentially sodium free.

The other ingredients are amino acid proline and water for injections.

What PRIVIGEN looks like and contents of the pack:

PRIVIGEN is presented as a solution for infusion.

The solution is clear or slightly opalescent and colourless to pale yellow.

Each glass infusion vial contains 25 ml, 50 ml or 100 ml solution for infusion.

Pack sizes: 1 vial per carton.

Not all pack sizes may be marketed.

Holder of certificate of registration:

Gen-Eye (Pty) Ltd[1]

Royal Palm Business Estate

Unit 7, 646 Washington Street

Halfway House, Midrand, 1685

Gauteng, South Africa

This leaflet was last revised in:

Not applicable

Registration number:

To be allocated

Access to the corresponding professional information:

The corresponding Professional Information is available electronically on www.geneye.co.za.

Alternatively, to obtain this Professional Information please contact Gen-Eye (Pty) Ltd on 011-312 3812 or email info@geneye.co.za.

[1] Company Registration Number.: 2009/009360/07