Package leaflet: Information for the user

Privigen 100 mg/ml (10%) solution for infusion
human normal immunoglobulin (IVIg)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or healthcare professional.
- If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Privigen is and what it is used for

What Privigen is

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.

How Privigen works

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.

What Privigen is used for

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 five 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

➔ Read this section carefully. The information given should be taken into consideration by you and your doctor before you are given Privigen.

Do **NOT** take Privigen

- 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

Which circumstances increase the risk of having side effects?

➔ 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), bluish skin (cyanosis), abnormally low level of oxygen in the blood (hypoxia), decrease in blood pressure (hypotension) and increased body temperature (fever). Symptoms typically appear during or within 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

➔ Tell your doctor or healthcare professional if you are using, have recently used or might use any other medicines.

The concomitant use of medicines that increase the excretion of water from your body (loop diuretics) should be avoided during treatment with Privigen. Your doctor will decide whether you should use or continue treatment with loop diuretics.

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 and breast-feeding

➔ Tell your doctor or healthcare professional if you are pregnant, plan to become pregnant or are breast-feeding. 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 it 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.

Sodium content
This medicine contains less than 2.3 mg sodium (main component of cooking/table salt) in 100 ml. This is equivalent to 0.12% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Privigen

Privigen is intended solely for the infusion into a vein (intravenous infusion). It is usually administered by your doctor or healthcare professional.
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 receive more Privigen than you should

Overdose is very unlikely to occur because Privigen is usually administered under medical supervision. If, in spite of this, 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. 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.

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 a hospital emergency room 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), pain, (including back pain, pain in extremities, 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 including haemolytic anaemia), $^{\beta}$ 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), upset stomach (nausea), vomiting, loose stools (diarrhoea), stomach pain, skin disorder (including rash, itching (pruritus), hives (urticaria), maculo-papular 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 (including infusion site discomfort).

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.

[β]The haemolytic anaemia cases after controlled clinical study completion were observed at significantly reduced frequency due to enhancements in the Privigen manufacturing process.

➔ If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet.

Please also refer to section 2 "What you need to know before you are given Privigen" for additional details on circumstances which increase the risk of side effects.

Reporting of side effects

If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

UK: Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2
Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie;
Email: medsafety@hpra.ie

Malta: ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Privigen

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton and the vial label after EXP. The expiry date refers to the last day of that month.
- Because the solution contains no preservative, your healthcare professional must infuse it immediately after opening the vial.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not use this medicine if you notice that the solution is cloudy or contains particles floating within the solution.

6. Contents of the pack and other information

What Privigen contains

- The **active substance** is human normal immunoglobulin (antibodies of the type IgG). Privigen contains 100 mg/ml (10%) human protein of which at least 98% is IgG.
  The approximate percentage of IgG subclasses is as follows:
  IgG_1 ..... 69%
  IgG_2 ..... 26%

IgG_3 ..... 3%
IgG_4 ..... 2%

This medicine contains trace amounts of IgA (not more than 25 micrograms/ml).

- The **other ingredients** (excipients) are the amino acid proline, water for injections, and hydrochloric acid or sodium hydroxide (for pH adjustment).

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.

Pack sizes:
1 vial (2.5 g/25 ml, 5 g/50 ml, 10 g/100 ml, 20 g/200 ml) or 40 g/400ml,
3 vials (10 g/100 ml or 20 g/200 ml).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom
CSL Behring UK Ltd.
Tel: +44 (0)1444 447405

Ireland
CSL Behring GmbH
Tel: +49 69 305 17254

Malta
AM Mangion Ltd.
Tel: +356 2397 6333

This leaflet was last revised in 11/2020.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Posology and method of administration

The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of injections**
Replacement therapy		
Primary immunodeficiency syndromes (PID)	starting dose: 0.4-0.8 g/kg bw	
	maintenance dose: 0.2-0.8 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 g/l
Secondary immunodeficiencies (as defined in section 4.1 of the SmPC)	0.2-0.4 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 g/l
Immunomodulation		
Primary immune thrombocytopenia (ITP)	0.8-1 g/kg bw	on day 1, possibly repeated once within 3 days
	or 0.4 g/kg bw/d	for 2 to 5 days
Guillain-Barré syndrome	0.4 g/kg bw/d	for 5 days
Kawasaki disease	2 g/kg bw	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)	starting dose: 2 g/kg bw	in divided doses over 2-5 days
	maintenance dose: 1 g/kg bw	every 3 weeks over 1-2 days
Multifocal motor neuropathy (MMN)	starting dose: 2 g/kg bw maintenance dose: 1 g/kg bw or 2 g/kg bw	over 2 to 5 consecutive days every 2 to 4 weeks or every 4 to 8 weeks over 2 to 5 days

Method of administration
For intravenous use.

Human normal immunoglobulin should be infused intravenously at an initial infusion rate of 0.3 ml/kg bw/hr for approximately 30 min. If well tolerated, the rate of administration may gradually be increased to of 4.8 ml/kg bw/hr.
In PID patients who have tolerated the infusion rate of 4.8 ml/kg bw/hr well, the rate may be further increased gradually to a maximum of 7.2 ml/kg bw/hr.
If dilution prior to infusion is desired, Privigen may be diluted with 5% glucose solution to a final concentration of 50 mg/ml (5%).

Special precautions

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.

It is strongly recommended that every time Privigen 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.

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in the section below.

Special precautions for disposal and other handling

The product should be brought to room or body temperature before use. A vented infusion line should be used for the administration of Privigen. Always pierce the stopper at its centre, within the marked area.

The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.
If dilution is desired, 5% glucose solution is recommended. For obtaining an immunoglobulin solution of 50 mg/ml (5%), Privigen 100mg/ml (10%) should be diluted with an equal volume of the glucose solution. Aseptic technique must be strictly observed during the dilution of Privigen.

Once the vial has been entered under aseptic conditions, its contents should be used promptly. Because the solution contains no preservative, Privigen should be infused as soon as possible. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.