Product Information

**Sandoglobulin®**

**Australia**

**NAME OF THE MEDICINE**

Human normal immunoglobulin for intravenous injection

**DESCRIPTION**

Sandoglobulin® is a sterile, lyophilised preparation for reconstitution, containing human gammaglobulin.

Sandoglobulin® is prepared from pooled venous plasma by the cold ethanol fractionation process, followed by treatment at pH 4.0 with the addition of a minimal quantity of pepsin (1:10,000 w/w). It is at least 96% pure.

The pooled plasma is obtained from healthy donors who must, as far as can be ascertained after clinical examination, laboratory tests on their blood and the study of their medical history, be free from detectable agents of infection transmissible by transfusion of blood or blood derivatives. In particular tests for hepatitis B surface antigen, antibodies directed to human immunodeficiency virus type 1 (HIV-1) or HIV-2 and hepatitis C virus (HCV) are carried out by suitable methods and must give negative results.

**SPECIAL WARNING**

Sandoglobulin® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and through the application of viral elimination/reduction steps.

The manufacturing process contains specific steps to reduce the possibility of virus transmission including pepsin/pH 4 treatment and nanofiltration. The current procedures applied in the manufacture of Sandoglobulin® are effective against HIV (human immunodeficiency virus), hepatitis B and hepatitis C virus, and the non-enveloped viruses, hepatitis A and parvovirus B19, as demonstrated in studies using relevant and model viruses.

Despite these measures, such products may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in such products. The physician should discuss the risks and benefits of this product with the patient.

Appropriate vaccination for patients in receipt of medicinal products derived from human blood or plasma should be considered.
Sandoglobulin® contains all the humoral IgG antibodies normally occurring in the donor pool. At least 90% of the immunoglobulin is monomeric (7S) and dimeric IgG, the latter accounting for only a very small percentage. The remainder consists of small amounts of polymeric IgG fragments and traces of IgA and IgM. The distribution of the IgG sub-classes corresponds to that of normal serum.

Each vial of the lyophilised preparation contains 6 g or 12 g protein and 10 g or 20 g sucrose as well as small quantities of sodium chloride. The preparation does not contain any preservative. The product is reconstituted with 0.9% saline to a sterile 3% or 6% solution.

**PHARMACOLOGY**

Sandoglobulin® contains a broad spectrum of antibody specificities against bacterial and viral antigens that are capable of both opsonisation and neutralization of pathogens. It is devoid of spontaneous anticomplementary activity while retaining its ability to activate complement once binding to specific antigen has occurred. It is essentially free of aggregates. Sandoglobulin® provides IgG antibodies for replacement therapy in immunodeficient patients. It has also been used successfully in some cases of idiopathic thrombocytopenic purpura (ITP), although the mechanism of action in ITP has not been fully elucidated.

The plasma half-life of Sandoglobulin® measured in normal subjects is about 15 days, although individual variations have been observed. The *in vivo* behaviour after intravenous injection in individual subjects has been found to correspond to that of standard intramuscular gammaglobulin. In immunodeficient patients, the half-life can be significantly greater than 15 days. Therefore this variable, as well as the size of the dose, is important in determining the frequency of dosing for each patient.

Sandoglobulin® is evenly distributed between the intravascular and the extravascular compartment and is catabolised at a rate proportional to the serum IgG concentration.

**INDICATIONS**

Sandoglobulin® is indicated in the treatment of primary antibody deficiency, such as in congenital agammaglobulinaemia, common variable hypogammaglobulinaemia and combined immunodeficiency.

Sandoglobulin® has been used successfully in the treatment of some cases of idiopathic thrombocytopenic purpura (ITP).

**CONTRAINDICATIONS**

Sandoglobulin® is contraindicated in individuals who are known to have had an anaphylactic or severe systemic response to normal human immunoglobulin. Individuals with the selective IgA deficiencies should not receive Sandoglobulin® or any immune globulin preparation.

**WARNINGS**

**Inflammatory Reactions**

Patients with agamma- or extreme hypogammaglobulinaemia may develop inflammatory reactions to Sandoglobulin®, especially following too rapid infusion and in previously untreated patients. The same phenomenon may occur in immunologically normal subjects during initial stages of infection. A rise in temperature, chills, nausea, vomiting and myalgia may result. The patient's vital signs should be monitored closely and continuously throughout the infusion.
Anaphylactic Reactions

Sandoglobulin® can on rare occasions cause anaphylactoid reactions in sensitive individuals, particularly in agammaglobulinaemic patients with chronic infections. Patients with agammaglobulinaemia or severe hypogammaglobulinaemia who have never received immunoglobulin replacement therapy, or whose time from last treatment is greater than 8 weeks, may be at risk of suffering from anaphylactoid reactions, occasionally leading to shock, when receiving intravenous immunoglobulin as a rapid infusion. In such patients, rapid infusion must be avoided. Vital signs should be monitored continuously and careful surveillance of the patient is required throughout the infusion. Adrenaline and other suitable supportive measures should be available for treatment of any anaphylactic reaction. Care should be taken when administering Sandoglobulin® to patients with paraproteins.

Very rarely, intravenous immunoglobulin may cause a precipitous fall in blood pressure associated with the clinical signs of anaphylaxis even in patients in whom previous administration of immunoglobulin preparations was well tolerated.

Since serious adverse reactions, which may be of the anaphylactoid type, occur either shortly after initiation of administration or often within the next 30 - 60 minutes, patients should be observed for at least 20 minutes after administration.

Hypersensitivity Reactions

Due to previous sensitisation of the recipient to certain antigens, hypersensitivity reactions may occur rarely, and usually in patients with selective IgA deficiency.

Effects on Renal Function

As with other intravenous immunoglobulin (IVIG) preparations, cases of transient increase in creatinine levels have been rarely reported after Sandoglobulin® administration, leading to acute renal failure in some patients. Patients at increased risk are those with pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis and paraproteinaemia, and those taking concomitant nephrotoxic drugs. Most patients presented with multiple risk factors and the majority were receiving intravenous immunoglobulin for the first time. More than 50% of the patients who developed acute renal failure received > 0.4 g/kg body weight per day. Although in most cases the increase in creatinine levels was mild, transient (5 - 12 days) and was noted 2 - 5 days after the infusion, supportive therapy may occasionally be required. Patients should be adequately hydrated prior to IVIG infusion and the recommended dose should not be exceeded. Renal function should be assessed prior to IVIG infusion and then at appropriate intervals in patients at increased risk of developing acute renal failure. The patient or guardian should be instructed to report noteworthy decreases in urine output. If renal function deteriorates, discontinuation of IVIG should be considered.

PRECAUTIONS

No other medications or fluids should be mixed with the Sandoglobulin® preparation for infusion. It should be administered by a separate infusion line.

Certain adverse reactions may occur more frequently
- In case of high rate of infusion,
- In patients with hypo- or agammaglobulinaemia with or without IgA deficiency,
- In patients who receive 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.
Aseptic meningeal irritation with transient alteration of cerebrospinal fluid has been reported after infusion of Sandoglobulin® and other immunoglobulin preparations, primarily in patients presenting with idiopathic thrombocytopenia and receiving high dose therapy. Cessation of treatment has resulted in remission within several days.

A few cases of generally mild haemolysis have been reported with Sandoglobulin® and other immunoglobulin products. The haemolysis was attributed to the transfer of blood-type antibodies with the immunoglobulin in the preparation and appears to be enhanced by concomitant blood transfusion.

**Use in Pregnancy**

Animal reproduction studies have not been conducted with Sandoglobulin®. It is also not known whether Sandoglobulin® can cause foetal harm when administered to pregnant women, or whether it can affect reproductive capacity. Sandoglobulin® should be given to a pregnant woman only if clearly indicated.

**Interactions**

The effectiveness of an active immunisation can be reduced by simultaneous treatment with intravenous immunoglobulin. Immunoglobulin administration may impair the efficacy of live-attenuated virus vaccines such as measles, rubella, mumps and varicella. Impairment can last up to 1 year. For children who receive doses of 0.4 g/kg intravenous immunoglobulin for repeat treatment, measles vaccine should be deferred for at least 8 months.

After the administration of immunoglobulin, the transitory rise in passively transferred antibodies into the patient's blood may lead to misleading positive results in serological testing.

**ADVERSE REACTIONS**

Due to the low content of aggregates, Sandoglobulin® is well tolerated and adverse reactions are infrequent. When administered correctly, adverse reactions occur in less than 1% of patients who are not immunodeficient. Patients naive to immunoglobulin usually experience a higher frequency of adverse events, including those of a minor nature, than patients who are well maintained on regular therapy.

Agammaglobulinaemic and hypogammaglobulinaemic patients who have never received immunoglobulin substitution therapy before, or whose time from last treatment is greater than 8 weeks, may show adverse reactions if the initial infusion flow rate exceeds 20 drops (1 mL) per minute. This occurs in approximately 10% of the cases (see “WARNINGS”). Thrombotic events have been reported in the elderly, in patients with signs of cerebral or cardiac ischaemia, and in overweight and severely hypovolaemic patients.

The majority of adverse reactions to intravenous immunoglobulins are inflammatory (phlogistic) in nature (see “WARNINGS”).
Reactions observed during or after the infusion:

**Common:** headache, weakness, fatigue, malaise, dizziness, pyrexia, chills, sweating, nausea, vomiting, diarrhoea, back pain, muscle pain, facial flushing, itching

**Uncommon:** abdominal pain, cyanosis, dyspnoea, feeling of tightness or pain in the chest, rigor, pallor, hypertension, hypotension, tachycardia.

The above symptoms may become apparent only 1/2 - 1 hour after the beginning of the infusion. In such cases the infusion should be stopped until the symptoms have subsided.

In a few patients, skin reactions including eczema have been observed several days after the administration of Sandoglobulin®.

Immediate anaphylactoid and hypersensitivity reactions may be observed in exceptional cases (see “WARNINGS”, “CONTRAINDICATIONS”). Severe hypotension, circulatory collapse and loss of consciousness are very rare events. If such reactions occur, the infusion should be discontinued until the symptoms have subsided, and supportive treatment may be indicated.

Very rarely, transient/reversible renal dysfunction and acute renal failure have been reported (see “WARNINGS”).

As with other IV immunoglobulin preparations, aseptic meningeal irritation and haemolysis have been reported in a limited number of patients (see “PRECAUTIONS”).

**DOSAGE AND ADMINISTRATION**

**Immunodeficiency:** 0.1-0.3 g per kg body weight administered by intravenous infusion at intervals of 3-4 weeks. If clinical response is inadequate the dosage may be increased or the interval decreased.

**Treatment of idiopathic thrombocytopenic purpura:** 0.4 g per kg body weight on 5 consecutive days.

**Administration**

Note: The solution must be clear and infused at close to body temperature. **Do not use if turbid.**

**For the first dose:** a 3% solution is infused at:
- 10-20 drops (0.5-1.0 mL)/min for 15 minutes
- 20-30 drops (1.0-1.5 mL)/min for the next 15 minutes
- 40-50 drops (2.0-2.5 mL)/min thereafter.

The subsequent doses on the same occasion are given at approximately 50 drops (2.5 mL)/min.

**For follow-up doses of 12 g and more:** use a 6% solution at the following rate:
- 20-30 drops (1.0-1.5 mL)/min for 15-30 minutes
- 40-50 drops (2.0-2.5 mL)/min thereafter.
Recent investigations confirm that Sandoglobulin® is well-tolerated and not likely to produce side effects when infused at these rates. However, the first infusion of Sandoglobulin® in previously untreated agammaglobulinaemic and hypogammaglobulinaemic patients may lead to systemic side effects. Some of the effects may occur as a result of a reaction between the antibodies administered and free antigen in the blood and tissues of the immunodeficient recipient. When free antigen is no longer present, further administration of Sandoglobulin® to immunodeficient patients as well as to normal individuals, does not cause further untoward side effects.

**Reconstitution**

The product is reconstituted with 0.9% NaCl (saline) solution to a sterile 3% or 6% solution. An aseptic technique should be used for reconstitution.

**Preparation of a 3% solution:**
- Dilute 6 g Sandoglobulin® with 200 mL 0.9% NaCl solution

**Preparation of a 6% solution:**
- Dilute 6 g Sandoglobulin® with 100 mL 0.9% NaCl solution
- Dilute 12 g Sandoglobulin® with 200 mL 0.9% NaCl solution.

Dissolution may be aided by intermittent gentle rotation of the bottle. The dissolution should be achieved in 20 minutes.

- Do not shake - avoid frothing. Frothing will denature the proteins contained in Sandoglobulin®, reduce their solubility and decrease the activity of the product.
- Use only clear solutions at close to body temperature.
- Use an in-line filter infusion set.
- After reconstitution, the preparation should be administered immediately. Any unused portion must be discarded.

**DO NOT SHAKE THE SOLUTION.**

**OVERDOSAGE**

No cases of overdose with Sandoglobulin® have been reported. Nevertheless overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

**PRESENTATION**

Sandoglobulin® is a sterile lyophilised preparation for reconstitution supplied in 6 g and 12 g vials.

Storage: Store below 25°C or refrigerate. Do not freeze. Protect from light. Do not use after expiry date. After reconstitution, the vial should be used promptly. Discard any unused portion.

**MANUFACTURED BY**

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POISON SCHEDULE OF THE MEDICINE
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