CSL Behring

Sandoglobulin® Liquid

Immune Globulin Intravenous (Human)

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
IV	12% Solution for infusion	L-proline, Ph.Eur./USP; L- Isoleucine, Ph.Eur./USP; and Nicotinamide, Ph.Eur./USP.

DESCRIPTION

Sandoglobulin® Liquid, Immune Globulin Intravenous (Human), is a clear or slightly opalescent, colorless or pale yellow solution of unmodified human immunoglobulin. The concentration of the active ingredient in Sandoglobulin® Liquid is 12%(120 g/L).

INDICATIONS AND CLINICAL USE

Sandoglobulin® Liquid, Immune Globulin Intravenous (Human), is indicated for the treatment of adult and pediatric patients with primary immune deficiency (PID) or secondary immune deficiency (SID) who require immunoglobulin replacement therapy.

Pediatrics (*4-18* years of age):

Patients younger than 18 years of age were included in all the clinical studies conducted in PID.

CONTRAINDICATIONS

Sandoglobulin® Liquid, Immune Globulin Intravenous (Human), is contraindicated in the following patients:

Patients who are hypersensitive to Immunoglobulin or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

Patients who are hypersensitive to homologous immunoglobulins, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA.

Sandoglobulin® Liquid contains the excipient L-isoleucine and L-proline and is contraindicated in patients with maple syrup urine disease (MSUD) and hyperprolinemia. See WARNINGS AND PRECAUTIONS.

WARNINGS AND PRECAUTIONS

General

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "DOSAGE AND ADMINISTRATION" 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 the case of high rate of infusion,
- in patients with hypo or agammaglobulinaemia with or without IgA deficiency,
- in patients who receive IVIg 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.

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 side effect.

In case of shock, the current medical standards for shock treatment should be observed.

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, HCV, and for the non-enveloped viruses 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 Sandoglobulin® Liquid, Immune Globulin Intravenous (Human), 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.

Endocrine and Metabolism

Sandoglobulin® Liquid contains the excipient L-isoleucine. Intake of L-isoleucine is contraindicated in patients with maple syrup urine disease (MSUD). This disease is a hereditary disorder of metabolism of oxidative decarboxylation. An increase of L-isoleucine may induce metabolic acidosis and may lead to cerebral damage.

Nicotinamide is a water soluble vitamin and forms an essential constituent of the normal human body. There is no known contraindication. Nicotinamide serum concentrations of 0.64 mmol/l measured after infusion of 1 g/kg b.w. of Sandoglobulin® Liquid is well tolerated. Higher serum concentrations may be associated with headache and nausea.

Sandoglobulin® Liquid also contains as excipient the non-essential amino acid L-proline and is therefore contraindicated in patients with hyperprolinemia. Hyperprolinemia is a very rare disease and there are only a few families known worldwide with hyperprolinemia. Hyperprolinemic patients show an increased concentration of proline in the plasma and an increased urinary excretion of proline, hydroxyproline and glycine. The medical consequences appear to be moderate in most cases, however, an increased incidence of renal disease is observed in some cases and neurological symptoms and disturbance of mental development in others.

Immune

True hypersensitivity reactions are rare. They can occur very seldomly in cases of IgA deficiency with anti-IgA antibodies.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Potential complications can often be avoided by ensuring:

- that patients are not sensitive to human normal immunoglobulin by first injecting the product slowly (<1 ml/kg/min);
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive 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.

Neurologic

Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

Renal

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, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In a clinical study in pediatric patients with acute ITP, a transient slight-to-moderate decrease in Hemoglobin (Hb) levels has been observed in some children after administration of Sandoglobulin® Liquid. It was most likely caused by the underlying disease, by a dilution effect and/or by repeated blood sampling. In these patients, a follow-up of Hb is recommended. Information on adverse reactions is provided in the section ADVERSE REACTIONS.

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.

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, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered. In addition, the product should be administered at the minimum concentration and infusion-rate practicable. Sandoglobulin® Liquid contains no carbohydrates like sucrose or maltose.

Special Populations

Pregnant Women: The safety of Sandoglobulin® Liquid for use in human pregnancy has not been established in controlled clinical trials, consequently, it should only be used in pregnant women when the benefits outweigh the risks associated with its use.

Nursing Women: Immunoglobulins are excreted into the milk. Sandoglobulin® Liquid should only be used in nursing woman when the benefits outweigh the risks associated with its use.

Monitoring and Laboratory Tests

After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D may cause a positive direct or indirect antiglobulin test (Coombs' test).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions such as chills, headache, fever, epistaxis, rhinitis, sinusitis, abdominal pain, vomiting, allergic reactions, nausea, arthralgia, diarrhea, pharyngitis, infections, bronchitis, coughing, dizziness, 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, isolated cases of reversible hemolytic anemia/hemolysis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed with IVIg.

Thrombotic events have been reported in the elderly, in patients with signs of cerebral or cardiac ischemia, and in overweight and severely hypovolemic patients.

For safety with respect to transmissible agents, see WARNINGS AND PRECAUTIONS.

Clinical Trial Adverse Drug Reactions

SAGL351 Study

A total of 34 patients were treated in a Phase III, randomized, double-blind, 6 month duration study conducted in patients with Primary Immunodeficiency Disorders. A total of 17 patients received Sandoglobulin® Liquid, Immune Globulin Intravenous (Human) and 17 patients received lyophilized Sandoglobulin®.

Table 1: Numbers of patients with AEs in most frequently affected SMTT body systems in the Phase III safety population

Indication	PID	SAGL
Treatment	IVIG F10	
No. of patients		
Included	17	17
With AEs	16	17
No. of AEs	94	117
Body system		
Body as a whole-general disorder	9	6
Central and peripheral nervous system disorders	6	6
Gastrointestinal system disorders	5	9
Respiratory system disorders	12	14
Skin and appendages disorders	3	4
Musculoskeletal system disorders	5	2
Hearing and vestibular disorders	4	2
Cardiovascular disorder, general	0	1
Urinary system disorders	0	2
Vision disorders	2	3
White cell and reticulo-endothelial system disorders	0	0
Application site disorder	1	3

IVIG-F10 = Sandoglobulin® Liquid; SAGL=Sandoglobulin®; SMTT=Ex-Sandoz Medical Terminology Thesaurus.

The overall AE profile was similar for Sandoglobulin® Liquid and Sandoglobulin®. Almost all patients experienced at least 1 AE. The most common AEs were in the system organ classes or body systems body as a whole, central and peripheral nervous system, and gastrointestinal, respiratory. AEs were most common in the respiratory system.

Table 2: Most frequently reported AEs in the Phase III safety population

Indication	PID	SAGL
Treatment	IVIG F10	
No. of patients		
Included	17	17
With AEs	16	17
No. of AEs	94	117
Event		
Headache	4	4
Fever	2	3
Epistaxis	1	1
Rhinitis	6	8
Abdominal pain	0	1
Influenza-like symptoms	4	2
Sinusitis	4	2
Vomiting	2	1
Arthralgia	3	1
Diarrhea	2	4
Infection	3	3
Nausea	1	1
Pharyngitis	2	3
Upper respiratory tract infection	3	6
Coughing	2	4
Dizziness	1	1
Bronchitis	1	3

IVIG-F10 = Sandoglobulin® Liquid; SAGL = Sandoglobulin®

The most common AEs in patients treated with Sandoglobulin® Liquid or Sandoglobulin® were rhinitis, upper respiratory tract infection, and headache.

ZLB04_005CR Study

A total of 42 patients were treated in an open-label, 6 month duration study to evaluate the safety and efficacy of Sandoglobulin® Liquid in patients with Primary Immunodeficiency Diseases. The AE profile for this study is presented below in Table 3 (no. of patients experiencing AEs by system organ class) and in Table 4 (Most frequent AEs).

Table 3: SOC most frequently (> 10% of patients) characterized by AEs (ITT population)

System organ class	No. (%) of patients N=42
Infections and infestations	27 (64.3)
Nervous system disorders	27 (64.3)
Respiratory, thoracic and mediastinal disorders	27 (64.3)
Gastrointestinal disorders	25 (59.5)
General disorders and administration site conditions	25 (59.5)
Musculoskeletal and connective tissue disorders	14 (33.3)
Eye disorders	6 (14.3)
Ear and labyrinth disorders	5 (11.9)
Skin and subcutaneous tissue disorders	5 (11.9)

ITT = Intent to treat data set; SOC = System organ class

Table 4: Most frequent (> 5% of patients) AEs (ITT population)

Preferred term	System organ class	No. (%) of patients N=42
Headache	Nervous system disorders	25 (59.5)
Pharyngolaryngeal pain	Respiratory, thoracic and mediastinal disorders	16 (38.1)
Sinusitis	Infections and infestations	12 (28.6)
Diarrhea	Gastrointestinal disorders	10 (23.8)
Fatigue	General disorders and administration site conditions	10 (23.8)
Nausea	Gastrointestinal disorder	10 (23.8)
Pyrexia	General disorders and administration site conditions	10 (23.8)
Arthralgia	Musculoskeletal and connective tissue disorders	9 (21.4)
Cough	Respiratory, thoracic and mediastinal disorders	9 (21.4)
Nasal congestion	Respiratory, thoracic and mediastinal disorders	8 (19.0)
Rhinorrhoea	Respiratory, thoracic and mediastinal disorders	7 (16.7)
Chills	General disorders and administration site conditions	6 (14.3)
Myalgia	Musculoskeletal and connective tissue disorders	6 (14.3)
Nasopharyngitis	Infections and infestations	6 (14.3)
Pain	General disorders and administration site conditions	6 (14.3)
Abdominal pain	Gastrointestinal disorders	5 (11.9)
Abdominal pain upper	Gastrointestinal disorders	5 (11.9)
Sinus headache	Nervous system disorders	5 (11.9)
Vomiting	Gastrointestinal disorders	5 (11.9)
Chest pain	General disorders and administration site conditions	4 (9.5)
Dizziness	Nervous system disorders	4 (9.5)
Ear pain	Ear and labyrinth disorders	4 (9.5)
Sinus congestion	Respiratory, thoracic and mediastinal disorders	4 (9.5)
Toothache	Gastrointestinal disorders	4 (9.5)
Upper respiratory tract infection	Infections and infestations	4 (9.5)
Asthma	Respiratory, thoracic and mediastinal disorders	3 (7.1)

Abnormal Hematologic and Clinical Chemistry Findings

The laboratory data from the Phase III clinical trials did not indicate any significant changes in the variables analyzed in patients treated with either Sandoglobulin® Liquid or Sandoglobulin®.

DRUG INTERACTIONS

Overview

The administration of Sandoglobulin® Liquid, Immune Globulin Intravenous (Human), in patients with epilepsy should be carefully monitored. Co-administration of phenytoin together with high doses of Sandoglobulin® Liquid might induce hepatic toxicity, as shown by elevated enzyme levels. Although this effect is considered to be due to phenytoin activity, a contribution of the nicotinamide present in Sandoglobulin® Liquid cannot be excluded.

Nicotinamide present in Sandoglobulin® Liquid may interact with the metabolism of primidone and carbamazepine.

Interactions of nicotinamide with cardiac drugs such as B-blockers and vasodilators in humans are not known.

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 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.

Incompatibilities

Sandoglobulin® Liquid must not be mixed with other medical products in the same infusion line.

Drug-Laboratory Interactions

Interference with serological testing

After infusion 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 allo-antibodies (e.g. Coombs' test), reticulocyte count and haptoglobin.

DOSAGE AND ADMINISTRATION

Posology, Dosing Consideration and Adjustments

Sandoglobulin® Liquid, Immune Globulin Intravenous (Human), replaces missing IgG antibodies in primary and secondary immunodeficiency syndromes.

In replacement therapy the dosage may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. The daily dose should not exceed 1 g/kg. The following dosage regimens are given as a guideline.

Replacement therapy in primary and secondary immunodeficiency syndromes

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4 - 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 followed by at least 0.2 g/kg every three weeks.

The dose required to maintain a trough level of 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 2 - 4 weeks.

Trough levels should be measured in order to adjust the dose and dosage interval.

The dosage recommendations are summarized in the following **Table 5:**

Indication	Dose	Frequency of injections
Replacement therapy in primary and secondary immunodeficiencies	- starting dose: 0.4-0.8 g/kg bw - thereafter: 0.2 - 0.8 g/kg bw	every 2- 4 weeks to obtain IgG trough level of at least 4 - 6 g/l

Missed Dose

A missed dose should be administered as soon as possible to ensure an adequate IgG serum level.

Administration

Rapid infusion of concentrated IVIG products may cause side effects, particularly in patients who are naive to IVIG. It is therefore recommended that in such patients Sandoglobulin® Liquid be infused at an initial rate of 0.3 mL/kg/h for 60 minutes. If well tolerated, the rate may be gradually increased to a maximum of 1 mL/kg/h. In patients previously exposed to an IVIG product, Sandoglobulin® Liquid can be infused at an initial rate of 0.5 mL/kg/h for 30 minutes. If well tolerated, the rate may be gradually increased to a maximum of 1 mL/kg/h or 2 mg/kg/min.

Reconstitution

Not applicable. Sandoglobulin® Liquid is a ready-to-use liquid formulation.

OVERDOSAGE

Consequences of an overdose are not known.

ACTION AND CLINICAL PHARMACOLOGY

Immunoglobulins have a well-established history of safety and efficacy in humans. The antibodies contained in Sandoglobulin® Liquid, Immune Globulin Intravenous (Human), representing endogenous IgG, are natural components of the human body.

Pharmacodynamics

Sandoglobulin® Liquid contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Sandoglobulin® Liquid 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.

Pharmacokinetics

Sandoglobulin® Liquid 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 the intra- and extravascular compartments. Sandoglobulin® Liquid has a half-life of about 23 ± 13 days in normal adults. In a controlled PID study (n=17) comparing Sandoglobulin® Liquid with Sandoglobulin® using a dose of 0.3 - 0.8 g/kg bw IgG per month, comparable median half-lives were obtained: 34 days versus 41.5 days respectively. These results are also comparable with published data.

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

Duration of Effect

Patients with PID generally need life-long replacement therapy with immunoglobulins (Sandoglobulin® Liquid). The duration of the treatment effect, e.g. the prevention of recurrent infections depends on continual infusions of appropriate doses of immunoglobulins at regular intervals. Clinical experience with different immunoglobulins including Sandoglobulin® Liquid has shown that in the majority of patients, intervals between infusions of 3 - 4 weeks and monthly doses of 0.2 - 0.8g/kg bw are optimal. However, dosages and intervals have to be tailored to the clinical needs of the individual patient.

STORAGE AND STABILITY

Special precautions for storage

Store at 2 - 8°C, protect from light. Do not freeze. Store in the original package.

Shelf-life

Shelf-life is 32 months from the date of manufacture.

Shelf-life after first opening: Sandoglobulin® Liquid contains no preservative. From a microbiological point of view, the product should be used immediately.

SPECIAL HANDLING INSTRUCTIONS

The product should be brought to room temperature before use. The product should not be shaken. As with all parenteral solutions, the product should be inspected visually for particulate matter, turbidity and discoloration, prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. A slight yellow discoloration is of no concern and can be disregarded. A separate infusion line set should be used for administration.

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form:

Solution for infusion (12% solution). Sandoglobulin® Liquid is a clear or slightly opalescent, colorless or pale yellow solution of unmodified human immunoglobulin.

Composition for the 6g, 50 mL vial:

Immunoglobulin (Human):	6g
L-proline:	690 mg (120 mmol/L)
L-isoleucine:	654 mg (100 mmol/L)
Nicotinamide:	486 mg (80 mmol/L)
Water for injection:	ad 50 mL

Composition for the 12g, 100 mL vial:

Immunoglobulin (Human):	12g
L-proline:	1380 mg (120 mmol/L)
L-isoleucine:	1308 mg (100 mmol/L)
Nicotinamide:	972 mg (80 mmol/L)
Water for injection:	ad 100 mL

Packaging:

Sandoglobulin® Liquid is available in individual single use vials of 50 mL (6g) or 100 mL (12g).

Container: Clear type II glass infusion bottle with a grey chlorobutyl-rubber stopper and aluminium crimp cap with plastic flip-off disk as tamper-evident seal.

Packed by:

Benta SAL
Dbayeh - Lebanon
Under license from
CSL Behring AG
Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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