PRODUCT MONOGRAPH

Sandoglobulin® NF Liquid

Immune Globulin Intravenous (Human)

12 % Solution for infusion

Passive Immunizing Agent

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Immune Globulin Intravenous (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

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® NF 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® NF Liquid is 12% (120 g/L).

INDICATIONS AND CLINICAL USE

Sandoglobulin® NF 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® NF 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® NF 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® NF 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® NF 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 1g/kg b.w. of Sandoglobulin® NF Liquid is well tolerated. Higher serum concentrations may be associated with headache and nausea.

Sandoglobulin® NF 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® NF 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® NF Liquid contains no carbohydrates like sucrose or maltose.

Special Populations

Pregnant Women: The safety of Sandoglobulin® NF 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® NF 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® NF 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**	
Treatment	**IVIG-F10**	**SAGL**
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® NF Liquid; SAGL = Sandoglobulin®; SMTT = Ex-Sandoz Medical Terminology Thesaurus

The overall AE profile was similar for Sandoglobulin® NF 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**	
Treatment	**IVIG-F10**	**SAGL**
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® NF Liquid; SAGL = Sandoglobulin®

The most common AEs in patients treated with Sandoglobulin® NF 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 Sandogloblin NF 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® NF Liquid or Sandoglobulin®.

DRUG INTERACTIONS

Overview

The administration of Sandoglobulin® NF Liquid, Immune Globulin Intravenous (Human), in patients with epilepsy should be carefully monitored. Co-administration of phenytoin together with high doses of Sandoglobulin® NF 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® NF Liquid cannot be excluded.

Nicotinamide present in Sandoglobulin® NF 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® NF 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® NF 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 1g/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® NF 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® NF 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® NF 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® NF Liquid, Immune Globulin Intravenous (Human), representing endogenous IgG, are natural components of the human body.

Pharmacodynamics

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

Sandoglobulin® NF 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® NF 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® NF Liquid has a half-life of about 23 ± 13 days in normal adults. In a controlled PID study (n = 17) comparing Sandoglobulin® NF 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 NF 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® NF 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, protected from light. Do not freeze. Prior to the expiration date, the product can be held for a single storage period at room temperature (up to 25°C) for a maximum of 6 months, after which unused product must be discarded.

Shelf-life

Shelf-life is 32 months at 2 - 8°C, protected from light. However, the product can be exposed to up to 25°C for 6 months by the end consumer.

Shelf-life after first opening: Sandoglobulin® NF 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® NF 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):	6 g
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):	12 g
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® NF Liquid is available in individual single use vials of 50 mL (6g) or 100 mL (12 g).

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Human normal immunoglobulin

Chemical name: Polyvalent human immunoglobulin G

Molecular formula and molecular mass: 146,000 Da (IgG_1, IgG_2, and IgG_4) 170,000 Da (IgG_3)

Structural formula: IgG has two identical light polypeptide chains and two identical heavy polypeptide chains which are linked together with disulphide bonds. There are two intrachain disulphide bonds in the light chain, one in the variable region and one in the constant region. There are four such bonds in the heavy chain. Each disulphide bond encloses a peptide loop of 60-70 amino acid residues. These result in a series of globular regions with very similar secondary and tertiary structure. The peptide loops enclosed by the disulphide bonds represent the central portion of a domain of about 110 amino acid residues. In both the heavy and light chains the first of these domains corresponds to the variable region. In the light chain there is one additional domain and in the heavy chain three additional domains which make up the constant portion of the chain. It is variations in the amino acid sequence of the variable domains of the light and heavy chains that confers the specificity of immunoglobulins. The number and distribution of interchain disulphide bonds differ between the IgG subclasses with two for IgG_1 and IgG_4, four for IgG_2, and fifteen for IgG_3.

Physicochemical properties:

Property	Immunoglobulin G Subclass			
	IgG_1	**IgG_2**	**IgG_3**	**IgG_4**
Heavy chain	γ_1	γ_2	γ_3	γ_4
Mean serum concentration (mg/mL)	9	3	1	0.5
Sedimentation constant	7s	7s	7s	7s
Molecular weight ($x10^3$)	146	146	170	146
Half-life in humans (days)	21	20	7	21
Intravascular distribution (%)	45	45	45	45
Carbohydrate (%)	2-3	2-3	2-3	2-3
Valency for antigen binding	2	2	2	2
% total immunoglobulin	80			

Product Characteristics

The concentration of the active ingredient in Sandoglobulin® NF Liquid, Immune Globulin Intravenous (Human), is 12% (120 g/l). At least 96% (typically 99%) of the total protein is IgG (at least 90% of it exists as monomers and dimers). The product contains further small amounts of IgG fragments (≤ 10%), aggregates (≤ 2% commonly only 0.5%), albumin (≤ 3%) and traces of IgA and IgM. The level of IgA in the product is normally below 15 mg/l. The distribution of the IgG subclasses closely resembles that in normal human plasma.

The osmolality is approximately 360 mOsmol/kg and the product is therefore approximately isotonic. The pH value of the ready-to-use solution is 5.3 and the solution contains no buffer substances.

The preparation contains traces of sodium chloride (≤ 10 mmol/l). Sandoglobulin® NF Liquid contains no preservatives.

Excipients: L-Proline, L-Isoleucine and Nicotinamide are used as stabilizers.

The stabilizers, in particular nicotinamide, minimize the formation of IgG dimers, which is important for the tolerability of the product. The preparation contains traces of sodium chloride. Sandoglobulin® NF Liquid contains no carbohydrates or preservatives.

Viral Inactivation

The process steps that contribute to the viral safety include (1) separation of Filtrate B from Precipitate B, (2) suspension of Precipitate GG and 1st clarifying filtration, (3) nanofiltration, (4) pH 4/pepsin treatment, (5) DEAE-Sephadex batch adsorption chromatography and 2nd clarifying filtration, and (6) aluminum hydroxide batch adsorption and 3rd clarifying filtration. Viral reduction/inactivation studies on the above process steps have demonstrated total $\log_{10}$ reduction factors of >28 (human immunodeficiency virus (HIV)), >27 (pseudorabies virus), >18 (bovine viral diarrhea virus), and >20 (bovine enterovirus).

CLINICAL TRIALS

Study demographics and trial design

Table 6: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study patients (n=number)	Mean age (Range)	Gender
SAGL351	MC, R, DB, AC, PG, Phase III study in PID	0.2 to 0.8 g/kg bw IgG per month i.v. at a 2, 3 or 4-week interval, depending on patient requirements 6 months	17	32.3 (12-59)	7 M 10 F
ZLB04_005CR	MC, O, SA, Phase III study in PID	0.2 to 0.8 g/kg bw IgG*	42	32 (4-66)	29 M 13 F

AC = Active-controlled; DB = Double-blind; MC = Multicenter; O = Open; PG = Parallel group; R = Randomized; SA = Single arm; * Median dose received: 278.5 mg/kg to 800.7 mg/kg bw

The demographics and baseline characteristics were those anticipated in clinical practice.

A total of 34 patients were treated in a Phase III 6 month duration study, 17 patients received Sandoglobulin® NF Liquid, Immune Globulin Intravenous (Human), and 17 patients received Sandoglobulin. The previously approved, lyophilized formulation, Sandoglobulin®, was chosen as the comparator to Sandoglobulin® NF Liquid.

Table 7: Summary of Phase III studies in patients

Study designation	Investigational product	No. of patients	Comparator	No. of patients	Patient population
SAGL351	Sandoglobulin® NF Liquid	17	Sandoglobulin®	17	Patients with PID[a]
ZLB04_005CR	Sandoglobulin® NF Liquid	42	None	N/A	Patients with PID[b]

[a] Actual age range: 12-59 years.
[b] Actual age range: 4-66 years

Study SAGL351 was a multicentre, randomized, double-blind, active-controlled, parallel group, Phase III study in patients with PID. It was designed to compare the efficacy, pharmacokinetics,

tolerability, and safety of Sandoglobulin® NF Liquid with Sandoglobulin®.

Study ZLB04_005CR was a prospective, open, multicenter, single-arm study of Sandoglobulin NF Liquid in patients with PID. It was designed to assess the safety and efficacy of Sandoglobulin NF Liquid in patients with PID.

Study results

SAGL351:

The primary efficacy variable in Study SAGL351 was the number of days when a patient was out of school or work or unable to perform normal daily activities due to the underlying PID.

Table 8: Primary endpoint: Time lost (days) due to PID

Study	**SAGL351**		
Treatment	**Sandoglobulin® NF Liquid**	**Sandoglobulin®**	**Total**
ITT Population			
No. of patients	17	17	34
Any days off?			
Yes	10	9	19
No	7	8	15
p-value[a]	1.00		
Monthly average (days)			
Mean ± S.D.	0.72 ± 1.03	0.64 ± 0.95	0.68 ± 0.98
Median	0.3	0.3	0.3
Range	0-3.7	0-3.0	0-3.7
p-value[b]	0.75		
PP Population			
No. of patients	16	17	33
Any days off?			
Yes	10	9	19
No	6	8	14
p-value[a]	0.73		
Monthly average (days)			
Mean ± S.D.	0.77 ± 1.05	0.64 ± 0.95	0.70 ± 0.99
Median	0.3	0.3	0.3
Range	0-3.7	0-3.0	0-3.7
p-value[b]	0.61		

[a] Fisher's exact test.
[b] Wilcoxon rank sum test.

ZLB04_005CR:

The primary endpoint in study ZLB04_005CR was to demonstrate safety by evaluation of the number of infusions of IVIG-F10 temporally associated with AEs regardless of relationship during a treatment period of 6 months. AES were considered temporally associated if they started any time after the start of the infusion until 48 hours after the end of the infusion. For the study to be considered as having a positive outcome, the upper bound of the 95% confidence interval (CI) of the proportion of infusions temporally associated with one or more AEs had to be < 0.4%.

The proportion of infusions with temporally associated with adverse events was 0.32. The corresponding upper bound of the 2-sided 95% CI was 0.394, and thus, the primary objective of the study was met.

During the 6-month study period, there were no episodes of acute serious bacterial infection (aSBI) defined as pneumonia, meningitis, bacteremia/septicemia, osteomyelitis, septic arthritis, and visceral abscess. The annualized rate of aSBIs was 0.0 with an upper 1-sided 97.5% CI of 0.195 for the SDS/ITT population.

The annualized rate of days out of work, school, kindergarten, or daycare, or without the ability to perform normal activities, was 5.61 days. Seventeen of the 42 patients in the ITT population missed work, school, kindergarten, or daycare, or were unable to perform normal activities. The annualized rate of days hospitalized was approximately 0.9 days. Five patients were hospitalized.

DETAILED PHARMACOLOGY and TOXICOLOGY

Sandoglobulin® NF Liquid, Immune Globulin Intravenous (Human), could not be meaningfully tested in pharmaco-toxicology studies in animals, due to the xenoreactivity of human IgG to tissue epitopes of other species.

Nevertheless, human immunoglobulin formulations, have well established history of clinical safety and efficacy in patients, based on extensive use over many years. The antibodies contained in Sandoglobulin® NF Liquid, representing endogenous IgG, are natural components of the human body and can therefore be considered non-toxic. Therefore, safety testing in animal models, other than in a local tolerance study, in addition to not being considered feasible, is not considered necessary.

In the local tolerance study in rabbits, Sandoglobulin® NF Liquid or IVIG-F10 (0.3 ml per injection) was shown not to cause any significantly increased (quantitative and qualitative) local reactions at the intra-venous, peri-venous and intra-arterial application sites of the right ears of rabbits, in comparison with the left “control” ears treated similarly with saline. After 8 days, there were no treatment-related pathology findings.

The pharmacology, pharmacokinetics and toxicology of the excipient mixture containing nicotinamide, L-isoleucine and L-proline were investigated with in vitro and in vivo studies. The excipient mixture was generally well tolerated.

MICROBIOLOGY

Not Applicable.

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PART III: CONSUMER INFORMATION

Sandoglobulin® NF Liquid
Immune Globulin Intravenous (Human)

This leaflet is part III of a three-part "Product Monograph" published when **Sandoglobulin® NF Liquid** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Sandoglobulin® NF Liquid**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Sandoglobulin® NF Liquid contains "immunoglobulins" which are antibodies found in the blood. Immunoglobulins are produced by the body's immune system to fight infections caused by bacteria and viruses. If you have a shortage of antibodies you may not be able to fight off diseases.

What the medication is used for:

Sandoglobulin® NF Liquid is a prescription medication used to treat adults and children who need antibody replacement therapy due to Primary or Secondary Immune Deficiencies (conditions where your antibody levels are low, referred to as immunodeficiency).

What it does:

Sandoglobulin® NF Liquid increases your levels of antibodies (in cases of Primary or Secondary Immunodeficiencies).

When it should not be used:

If you have had an allergic reaction, skin rash, swelling of the face, wheezing or difficulty breathing to any of the components of **Sandoglobulin® NF Liquid** or to homologous immunoglobulins, especially in very rare cases of immunoglobulin A deficiency when you have been told you have antibodies to immunoglobulin A.

If you have maple syrup urine disease you should not take **Sandoglobulin® NF Liquid** as it contains L-isoleucine. This is a very rare disease which is caused by the inability to metabolize (eliminate) L-isoleucine.

If you have hyperprolinemia you should not take **Sandoglobulin® NF Liquid** as it contains L-proline. This is a very rare disease which is caused by the inability to metabolize (eliminate) L-proline.

What the medicinal ingredient is:

Immune Globulin Intravenous (Human)

What the important nonmedicinal ingredients are:

- L-Isoleucine, Ph.Eur./USP;
- L-proline, Ph.Eur./USP;
- Nicotinamide, Ph.Eur./USP.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

Sandoglobulin® NF Liquid is a solution for intravenous infusion.

It is supplied in 6 g (50 ml bottle) or 12 g (100 ml bottle) filling sizes. The concentration of the active ingredient (Immune Globulin Intravenous (Human)) is 12% or 120 g/L.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Sandoglobulin® NF Liquid** is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because **Sandoglobulin® NF Liquid** is made from human blood, there may be a risk of transmission of infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent.

- Developing allergic reactions which may include fever, chills, nausea, and vomiting are possible. On very rare occasions these reactions may lead to shock.

BEFORE you use **Sandoglobulin® NF Liquid** talk to your doctor or pharmacist if:

- You have hypogammaglobulinaemia or agammaglobulinaemia with or without immunoglobulin A deficiency
- This is your first treatment with any human normal immunoglobulin or it has been longer than 8 weeks since you had your last treatment
- You have diabetes
- You have epilepsy or are taking phenytoin
- You have kidney disease
- You have hypovolemia
- You are overweight
- You are over 65

Pregnancy:

Ask your doctor for advice before taking any medicine.

Breast-feeding:

Ask your doctor for advice before taking any medicine.

Important information about some of the ingredients in Sandoglobulin® NF Liquid:

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, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include 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 or 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 and parvovirus B19 viruses.

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

It is strongly recommended that every time you receive a dose of **Sandoglobulin® NF Liquid** the name and batch number of the product are recorded in order to maintain a record of the batches used.

Taking/using other medicines:
Please inform your doctor if you are taking, or have recently taken, any other medicine, including any products either bought or prescribed.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with **Sandoglobulin® NF Liquid** include the following anticonvulsants used in the treatment of epilepsy:

- Phenytoin
- Primidone
- Carbamazepine

Vaccines:
Please inform your doctor if you are planning to have a vaccination. **Sandoglobulin® NF Liquid** can impair the efficacy of certain live attenuated virus vaccines, such as measles, rubella, mumps and varicella for a period of at least 6 weeks and up to 3 months. After receiving this product, a period of 3 months should be allowed before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may continue for up to 1 year, so patients receiving the measles vaccine should have their antibody status checked.

Interference with serological testing:

Passive spread of antibodies to erythrocyte (red blood cell) antigens may interfere with some blood tests which detect the presence of antibodies e.g. Coombs test. Prior to any blood tests please inform your doctor you have received this product.

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor or nurse will usually give you your **Sandoglobulin® NF Liquid** by intravenous infusion.

Your doctor will work out the correct dose and dosing intervals of **Sandoglobulin® NF Liquid** for you depending on your body weight and why you need to take **Sandoglobulin® NF Liquid**.

Overdose:
If you think you have been given too many infusions or the infusion is going in too quickly, talk to a doctor or nurse immediately.

Missed Dose:
If you miss a dose contact your doctor for instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines **Sandoglobulin® NF Liquid** can have side effects.

Some people may develop adverse reactions such as chills, headache, fever, nausea, vomiting, allergic reactions, arthralgia (pain in a joint), low blood pressure, moderate low back pain, thrombotic events and acute renal failure.

Rarely, human normal immunoglobulins may cause anaphylactic shock which is a life-threatening allergic reaction characterised by swelling of body tissue, difficulty in breathing and sudden fall in blood pressure. If this happens your doctor or nurse should be informed immediately.

Cases of reversible aseptic (not caused by a bacteria) meningitis or inflammation of the membrane that envelops the brain and spinal cord, have been seen. The symptoms to watch for include: Malaise, fever, headache which can be severe, stiffness of the neck and back, nausea, vomiting, drowsiness, photophobia, painful eye movement.

Isolated cases of reversible haemolytic anaemia/haemolysis (where you have too few red blood cells caused either by red blood cells dying early or dying because their cell membrane has been disrupted) have been reported. The symptoms to watch for include: Fatigue, weakness, dizziness, headache, rapid heartbeat, ringing in the ears.

Also, rare cases of temporary inflammation/redness of the skin have been reported.

Tell your doctor or nurse if you suffer from any of these effects or from any other side-effect not mentioned in this leaflet.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

The following symptoms are common. If any of the listed symptoms occur, are severe of if they worry you, talk to your doctor or pharmacist:

- Chills
- Headache
- Fever
- Nausea
- Vomiting
- Allergic reactions (hives, skin redness, swelling of the mouth, lips or throat)
- Diarrhea
- Infections
- Dizziness
- Low blood pressure (manifested by dizziness and faintness)
- Joint pain
- Abdominal pain
- Moderate to low back pain

The following symptoms occur rarely but if they occur, you need to talk to your doctor or pharmacist about them:

- Aseptic meningititis: This is an inflammation of the membrane that envelops the brain and spinal cord, which is not caused by bacteria. The symptoms to watch for include: Malaise, fever, headache which can be severe, stiffness of the neck and back, nausea, vomiting, drowsiness, photophobia, painful eye movement.
- Temporary inflammation or redness of the skin

If the following rare symptoms occur, stop your medication and call your doctor or pharmacist without delay:

- Sudden fall in blood pressure (manifested by dizziness and faintness);
- Anaphylactic shock: A rapid occurring severe allergic reaction that involves the whole body. The symptoms to watch for are: Hives, swelling of the lips, tongue or throat, difficulty in breathing, low blood pressure, faintness, abdominal pain, nausea and vomiting.
- Hemolytic anemia/hemolysis (where you have too few red blood cells caused either by red blood cells dying early or dying because their cell membrane has been disrupted). The symptoms to watch for include: Fatigue, weakness, dizziness, headache, rapid heartbeat, ringing in the ears.

This is not a complete list of side effects. For any unexpected effects while taking **Sandoglobulin® NF Liquid**, *contact your doctor or pharmacist.*

HOW TO STORE IT

Store at 2 to 8°C and protect from light, by keeping **Sandoglobulin® NF Liquid** in its original packaging. Do not freeze. Do not use after the expiration date printed on the label. Prior to the expiration date, the product can be held for a single storage period at room temperature (≤ 25 °C) for a maximum of 6 months, after which unused product must be discarded.

Do not use **Sandoglobulin® NF Liquid** if it is cloudy or has deposits.

Keep **Sandoglobulin® NF Liquid** out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca*****

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

***** ***We recommend that CSL Behring Canada be copied when reporting suspected side effects, at the following address:***

adversereporting@cslbehring.com

or be informed by pager
Pager Number: 1-613-783-1892

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.cslbehring.com

or for more information you may communicate with the sponsor, CSL Behring Canada at: 1-613-783-1892

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