NOVARTIS

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IMMUNE GLOBULIN INTRAVENOUS (HUMAN) SANDOGLOBULIN®

Lyophilized Preparation

Rx only

DESCRIPTION

Immune Globulin Intravenous (Human), (IGIV) Sandoglobulin®, is a sterile, highly purified polyvalent antibody product containing in concentrated form all the IgG antibodies which regularly occur in the donor population (1). This immunoglobulin preparation is produced by cold alcohol fractionation from the plasma of volunteer US donors. Part of the fractionation may be performed by another US-licensed manufacturer. The fractionation process by which Sandoglobulin® is prepared from plasma includes several filtration steps which are carried out in the presence of filter aids; some of these filtration steps are used for the separation of a cold ethanol precipitate. Four of these steps were validated for virus *elimination.* The cumulative LRFs (log_{10} of reduction factors) were 15.5 for HIV (human immunodeficiency virus), 16.0 for PRV (pseudorabies virus), 9.3 for SFV (Semliki Forest virus), 12.4 for Sindbis virus, and 14.1 for BEV (bovine enterovirus). Sandoglobulin® is made suitable for intravenous use by treatment at acid pH in the presence of trace amounts of pepsin (2,3). Treatment with pepsin at pH4 rapidly *inactivates* enveloped viruses. LRFs were =6.1 for HIV, =5.3 for PRV, =4.4 for BVDV (bovine viral diarrhea virus), and =6.8 for SFV. PRV and the two model viruses for HCV (hepatitis C virus), BVDV and SFV, were all inactivated within 1/10, and HIV within 1/2 of the total incubation time used during production of Sandoglobulin®. *Overall viral clearance* by either *elimination* and/or *inactivation* during the manufacturing process has been documented to be =21 for HIV, =19 for PRV, =15 for SFV, and =14 for BEV (expressed as LRF). The preparation contains at least 96% of IgG and after reconstitution with a neutral unbuffered diluent has a pH of 6.6 ± 0.2. Most of the immunoglobulins are monomeric (7 S) IgG; the remainder consists of dimeric IgG and a small amount of polymeric IgG, traces of IgA and IgM and immunoglobulin fragments (4). The distribution of the IgG subclasses corresponds to that of normal serum (5,6,7,8). Final container lyophilized units are prepared so as to contain 1, 3, 6, or 12 g protein with 1.67 g sucrose and less than 20 mg NaCl per gram of protein. The lyophilized preparation is devoid of any preservatives and may be reconstituted with sterile water, 5% dextrose or 0.9% saline to a solution with protein concentrations ranging from 3%-12%. The patient's fluid, electrolyte, caloric requirements and renal function should be considered in selecting an appropriate diluent and concentration.

Table 1
Calculated Sandoglobulin® Osmolality (mOsm/kg)

	Concentration			
Diluent	**3%**	**6%**	**9%**	**12%**
0.9% NaCl	498	690	882	1074
5% Dextrose	444	636	828	1020
Sterile Water	192	384	576	768

CLINICAL PHARMACOLOGY

This product contains a broad spectrum of antibody specificities against bacterial, viral, parasitic, and mycoplasma antigens, that are capable of both opsonization and neutralization of microbes and toxins. The 3 week half-life of Immune Globulin Intravenous (Human), Sandoglobulin®, corresponds to that of Immune Globulin (Human) for intramuscular use, although individual variations in half-life have been observed (9,10). Appropriate doses of Sandoglobulin® restore abnormally low immunoglobulin G levels to the normal range. One hundred percent of the infused dose is available in the recipient's circulation immediately after infusion. After approximately 6 days, an equilibrium is reached between the intra- and extravascular compartments, with immunoglobulin G being distributed approximately 50% intravascular and 50% extravascular. In comparison, after the intramuscular injection of immune globulin, the IgG requires 2-5 days to reach its maximum concentration in the intravascular compartment. This concentration corresponds to about 40% of the injected dose (10).

While Sandoglobulin® has been shown to be effective in some cases of Immune Thrombocytopenic Purpura (ITP) (see *INDICATIONS AND USAGE*), the mechanism of action in ITP has not been fully elucidated.

Toxicity from overdose has not been observed on regimens of 0.4 g/kg body weight each day for 5 days (11,12,13). Sucrose is added to Sandoglobulin® for reasons of stability and solubility.

Since sucrose is excreted unchanged in the urine when given intravenously, Sandoglobulin® may be given to diabetics without compensatory changes in insulin dosage regimen. Please see *WARNINGS* section.

INDICATIONS AND USAGE

Immunodeficiency

Immune Globulin Intravenous (Human), Sandoglobulin®, is indicated for the maintenance treatment of patients with primary immunodeficiencies, e.g., in common variable immunodeficiency, severe combined immunodeficiency, and primary immunoglobulin deficiency syndromes such as X-linked agammaglobulinemia (12,14,15,16). Sandoglobulin® is preferable to intramuscular Immune Globulin (Human) preparations in treating patients who require an immediate and large increase in the intravascular immunoglobulin level (10), in patients with limited muscle mass, and in patients with bleeding tendencies for whom

intramuscular injections are contraindicated. The infusions must be repeated at regular intervals. Please see *DOSAGE AND ADMINISTRATION* section.

Immune Thrombocytopenic Purpura (ITP)

Acute

A controlled study was performed in children in which Immune Globulin Intravenous (Human), Sandoglobulin®, was compared with steroids for the treatment of acute (defined as less than 6 months duration) ITP. In this study, sequential platelet levels of 30,000, 100,000, and 150,000/µl were all achieved faster with Sandoglobulin® than with steroids and without any of the side effects associated with steroids (11,17). However, it should be noted that many cases of acute ITP in childhood resolve spontaneously within weeks to months. Sandoglobulin® has been used with good results in the treatment of acute ITP in adult patients (18,19,20). In a study involving 10 adults with ITP of less than 16 weeks duration, Sandoglobulin® therapy raised the platelet count to the normal range after a 5 day course. This effect lasted a mean of over 173 days, ranging from 30-372 days (21).

Chronic

Children and adults with chronic (defined as greater than 6 months duration) ITP have also shown an increase (sometimes temporary) in platelet counts upon administration of Immune Globulin Intravenous (Human), Sandoglobulin®, (17,21,22,23,24,25). Therefore, in situations that require a rapid rise in platelet count, for example prior to surgery or to control excessive bleeding, use of Sandoglobulin® should be considered. In children with chronic ITP, Sandoglobulin® therapy resulted in a mean rise in platelet count of 312,000/µl with a duration of increase ranging from 2-6 months (22,25). Sandoglobulin® therapy may be considered as a means to defer or avoid splenectomy (24,25,26). In adults, Sandoglobulin® therapy has been shown to be effective in maintaining the platelet count in an acceptable range with or without periodic booster therapy. The mean rise in platelet count was 93,000/µl and the average duration of the increase was 20-24 days (21,22). However, it should be noted that not all patients will respond. Even in those patients who do respond, this treatment should not be considered to be curative.

CONTRAINDICATIONS

As with all blood products containing IgA, Immune Globulin Intravenous (Human), Sandoglobulin®, is contraindicated in patients with selective IgA deficiency, who possess antibody to IgA. It may also be contraindicated in patients who have had severe systemic reactions to the intravenous or intramuscular administration of human immune globulin.

WARNINGS

WARNING

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death (27,28,29,30,31,32). Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

See *PRECAUTIONS* and *DOSAGE AND ADMINISTRATION* sections for important information intended to reduce the risk of acute renal failure.

Immune Globulin Intravenous (Human), 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 by inactivating and/or removing certain viruses. The fractionation process by which Sandoglobulin® is prepared from plasma includes several filtration steps which are carried out in the presence of filter aids; some of these filtration steps are used for the separation of a cold ethanol precipitate. Four of these steps were validated for virus *elimination.* The cumulative LRFs (log_{10} of reduction factors) were 15.5 for HIV (human immunodeficiency virus), 16.0 for PRV (pseudorabies virus), 9.3 for SFV (Semliki Forest virus), 12.4 for Sindbis virus, and 14.1 for BEV (bovine enterovirus). Sandoglobulin® is made suitable for intravenous use by treatment at acid pH in the presence of trace amounts of pepsin (2,3). Treatment with pepsin at pH4 rapidly *inactivates* enveloped viruses. LRFs were =6.1 for HIV, =5.3 for PRV, =4.4 for BVDV (bovine viral diarrhea virus), and =6.8 for SFV. PRV and the two model viruses for HCV (hepatitis C virus), BVDV and SFV, were all inactivated within 1/10, and HIV within 1/2 of the total incubation time used during production of Sandoglobulin®. *Overall viral clearance* by either *elimination* and/or *inactivation* during the manufacturing process has been documented to be =21 for HIV, =19 for PRV, =15 for SFV, and =14 for BEV (expressed as LRF). 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. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Novartis Pharmaceuticals, 973-781-7500. The physician should discuss the risks and benefits of this product with the patient.

Patients with agamma- or extreme hypogammaglobulinemia who have never before received immunoglobulin substitution treatment or whose time from last treatment is greater than 8 weeks, may be at risk of developing inflammatory reactions on rapid infusion of Immune Globulin Intravenous (Human), Sandoglobulin®, (over 20 drops [1 mL] per minute). These reactions are manifested by a rise in temperature, chills, nausea, and vomiting. The patient's vital signs should be monitored continuously. The patient should be carefully observed throughout the infusion, since these reactions on rare occasions may lead to shock. Epinephrine should be available for treatment of an acute anaphylactic reaction.

PRECAUTIONS

Please see *DOSAGE AND ADMINISTRATION* below, for important information on Immune Globulin Intravenous (Human), Sandoglobulin®, compatibility with other medications or fluids. Assure that patients are not volume depleted prior to the initiation of the infusion of IGIV. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of Sandoglobulin® and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product in fused per unit time by infusing Sandoglobulin® at a rate less than 2 mg Ig/kg/min.

Information for Patients

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with Immune Globulin Intravenous (Human), Sandoglobulin®. It is also not known whether Sandoglobulin® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sandoglobulin® should be given to a pregnant woman only if clearly needed (20).

Intact immune globulins such as those contained in Sandoglobulin® cross the placenta from maternal circulation increasingly after 30 weeks gestation (33,34). In cases of maternal ITP where Sandoglobulin® was administered to the mother prior to delivery, the platelet response and clinical effect were similar in the mother and neonate (20,34-43).

Pediatric Use

High dose administration of Immune Globulin Intravenous (Human), Sandoglobulin®, in pediatric patients with acute or chronic Immune Thrombocytopenic Purpura did not reveal any pediatric-specific hazard (11).

Antibodies in Immune Globulin Intravenous (Human) may impair the efficacy of live attenuated viral vaccines such as measles, rubella, and mumps (44,45,46). Immunizing physicians should

be informed of recent therapy with Immune Globulin Intravenous (Human) so that appropriate precautions may be taken.

Aseptic Meningitis Syndrome

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) (IGIV) treatment. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per cu.mm., predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

ADVERSE REACTIONS

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion. Progression to oliguria or anuria, requiring dialysis has been observed. Types of severe renal adverse events that have been seen following IGIV therapy include: acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis (27,28,29,30,31,32,47,57-59).

Inflammatory adverse reactions have been described in agammaglobulinemic and hypogammaglobulinemic patients who have never received immunoglobulin substitution therapy before or in patients whose time from last treatment is greater than 8 weeks and whose initial infusion rate exceeds 20 drops (1 mL) per minute. This occurs in approximately 10% of such cases. Such reactions may also be observed in some patients during chronic substitution therapy.

These reactions, which generally become apparent only 30 minutes to 1 hour after the beginning of the infusion, are as follows: flushing of the face, feelings of tightness in the chest, chills, fever, dizziness, nausea, diaphoresis, and hypotension. In such cases the infusion should be temporarily stopped until the symptoms have subsided.

Immediate anaphylactoid and hypersensitivity reactions due to previous sensitization of the recipient to certain antigens, most commonly IgA, may be observed in exceptional cases, described under *CONTRAINDICATIONS* (12,13,48).

In patients with ITP, who receive higher doses (0.4 g/kg/day or greater) 2.9% of infusions may result in adverse reactions (17). Headache, generally mild, is the most common symptom noted, occurring during or following 2% of infusions.

A few cases of usually mild hemolysis have been reported after infusion of intravenous immunoglobulin products (49,50). These were attributed to transferral of blood group (e.g., anti-D) antibodies (51,52).

DOSAGE AND ADMINISTRATION

It is generally advisable not to dilute plasma derivatives with other infusable drugs. Immune Globulin Intravenous (Human), Sandoglobulin®, should be given by a separate infusion line. No other medications or fluids should be mixed with the Sandoglobulin® preparation.

Sandoglobulin® should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65, volume depletion, paraproteinemia, sepsis, and patients receiving known nephrotoxic drugs).

In these cases especially it is important to assure that patients are not volume depleted prior to Sandoglobulin® infusion. No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum practicable. The product should be infused at a rate less than 2 mg Ig/kg/min.

Adult and Child Substitution Therapy

The usual dose of Immune Globulin Intravenous (Human), Sandoglobulin®, in immunodeficiency syndromes is 0.2 g/kg of body weight administered once a month by intravenous infusion. If the clinical response is inadequate, the dose may be increased to 0.3 g/kg of body weight or the infusion may be repeated more frequently than once a month (12,14,15,16).

The first infusion of Sandoglobulin® in previously untreated agammaglobulinemic or hypogammaglobulinemic patients must be given as a 3% immunoglobulin solution (use the total volume of fluid provided, or see *Table 2*, to reconstitute the lyophilized product). Start with a flow rate of 10-20 drops (0.5-1.0 mL) per minute. After 15-30 minutes the rate of infusion may be further increased to 30-50 drops (1.5-2.5 mL) per minute.

After the first bottle of 3% solution is infused and the patient shows good tolerance, subsequent infusions may be administered at a higher rate or concentration. Such increases should be made gradually allowing 15-30 minutes before each increment.

The first infusion of Sandoglobulin® in previously untreated agammaglobulinemic and hypogammaglobulinemic patients may lead to systemic side effects. The nature of these effects has not been fully elucidated. Some of them may be due to the release of pro-inflammatory cytokines by activated macrophages in immunodeficient recipients (53,54). Subsequent administration of Sandoglobulin® to immunodeficient patients as well as to normal individuals usually does not cause further untoward side effects.

Therapy of Idiopathic Thrombocytopenic Purpura (ITP)

Induction

0.4 g/kg of body weight on 2-5 consecutive days.

Acute ITP-Childhood

In acute ITP of childhood, if an initial platelet count response to the first two doses is adequate (30-50,000/µl), therapy may be discontinued after the second day of the 5 day course (17).

Maintenance-Chronic ITP

In adults and children, if after induction therapy the platelet count falls to less than 30,000/µl and/or the patient manifests clinically significant bleeding, 0.4 g/kg of body weight may be given as a single infusion. If an adequate response does not result, the dose can be increased to 0.8-1.0 g/kg of body weight given as a single infusion (18,55,56).

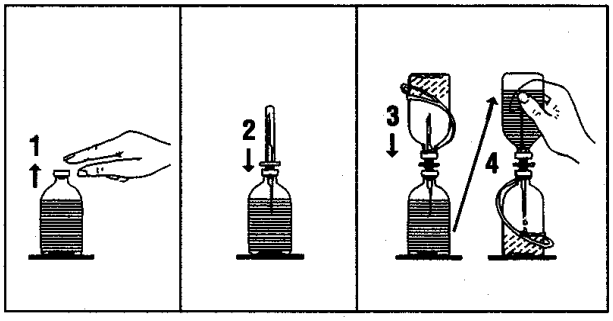
Reconstitution

For a 3% solution using the transfer set

1. Tear off the protective caps from the bottle containing the solvent and the Immune Globulin Intravenous (Human), Sandoglobulin®. Disinfect both rubber stoppers with alcohol.
2. Remove the protective cover from one end of the transfer set and insert the needle through the rubber stopper into the bottle containing the solvent.
3. Remove the cover from the other needle and plunge the inverted Sandoglobulin® bottle onto it, as shown in picture #3.
4. Invert the two bottles so that the solvent flows into the Sandoglobulin® bottle until the required amount (see *Table 2*, below) has been transferred.
5. Discard any unused solvent and the transfer set.

For a 6% solution using the transfer set

1. Follow steps 1-3 aforementioned.
2. Invert the two bottles so that the solvent flows into the Sandoglobulin® bottle. Use the appropriate amount (see *Table 2*, below) of solvent by removing the solvent bottle with transfer needle as soon as the fluid reaches the 6% mark printed on the Sandoglobulin® label.
3. Discard any unused solvent and the transfer set.



To reconstitute Sandoglobulin® from the individual vial package, or when using other diluents or higher concentrations, *Table 2* indicates the volume of sterile diluent required. Observing

aseptic technique, this volume should be drawn into a sterile hypodermic syringe and needle. The diluent is then injected into the corresponding Sandoglobulin®, vial size.

Table 2
Required Diluent Volume*

Concentration	1 g Vial	3 g Vial	6 g Vial	12 g Vial
3%	33.0 cc	100 cc	200 cc	**
6%	16.5 cc	50 cc	100 cc	200 cc
9%	11.0 cc	33 cc	66 cc	132 cc
12%	8.3 cc	25 cc	50 cc	100 cc

*In patients judged to be at increased risk of developing renal insufficiency, the concentration and infusion rate of Sandoglobulin® should be the minimum practicable.

**Container not large enough to permit this concentration

If large doses of Sandoglobulin® are to be administered, several reconstituted vials of identical concentration and diluent may be pooled in an empty sterile glass or plastic i.v. infusion container using aseptic technique.

Sandoglobulin® normally dissolves within a few minutes, though in exceptional cases it may take up to 20 minutes.

DO NOT SHAKE! Excessive shaking will cause foaming.

Any undissolved particles should respond to careful rotation of the bottle. Avoid foaming. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Filtering of Sandoglobulin® is acceptable but not required. Pore sizes of 15 microns or larger will be less likely to slow infusion, especially with higher Sandoglobulin® concentrations. Antibacterial filters (0.2 microns) may be used.

When reconstitution of Sandoglobulin® occurs outside of sterile laminar air flow conditions, administration must begin promptly with partially used vials discarded. When reconstitution is carried out in a sterile laminar flow hood using aseptic technique, administration may begin within 24 hours provided the solution has been refrigerated during that time. Do not freeze Sandoglobulin® solution.

PROCEED WITH INFUSION ONLY IF SOLUTION IS CLEAR AND AT APPROXIMATELY ROOM TEMPERATURE!

HOW SUPPLIED

Immune Globulin Intravenous (Human), Sandoglobulin®, is available as a white lyophilized powder in 1, 3, 6 and 12 g size vials. The only diluents which may be used to reconstitute the product are sterile (0.9%) Sodium Chloride Injection USP, 5% Dextrose, or Sterile Water.

Sandoglobulin® is available in individual vial packages.

1 g

Individual vial package (NDC 0078-0120-94)

3 g

Individual vial package (NDC 0078-0122-95)

6 g

Individual vial package (NDC 0078-0124-96)

12 g

Individual vial package (NDC 0078-0244-93)

Please see *Table 1* for Calculated Sandoglobulin® Osmolality (mOsm/kg).

Store and Dispense

Immune Globulin Intravenous (Human), Sandoglobulin®, should be stored at room temperature not exceeding 30ºC (86ºF). The preparation should not be used after the expiration date printed on the label.

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