Immunoglobulins SG Injection 5%

(Human Normal Immunoglobulin in Maltose (pH 4.25))

[COMPOSITION] Each 1mL contains
Human normal immunoglobulin G ..... 0.05 g
Maltose hydrate ..... 0.1 g
Water for injection ..... q.s.
The maximum IgA content is 60µg/mL.

[PRODUCT DESCRIPTION]
Colourless and transparent liquid in a colourless and transparent vial
Immunoglobulins SG Injection 5% is manufactured from human plasma donated by Singapore's voluntary and non-remunerated donors.

[INDICATIONS]
Replacement therapy in adults, children, and adolescents (0–18 years) in:
- Primary immunodeficiency syndromes (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of 4g/L

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, children and adolescents (0–18 years) in:
- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré syndrome
- Kawasaki disease (in conjunction with acetylsalicylic acid; see "Dosage and Administration")

[DOSAGE AND ADMINISTRATION]
IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.
Posology
The dose and dose regimen are dependent on the indication.
The dose may need to be individualised for each patient dependent on the clinical response. Dose based on body weight may require adjustment in underweight or overweight patients.
The following dose regimens are given as guidance.
Replacement therapy in primary immunodeficiency syndromes
The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/ L or within the normal reference range for the population age. 3–6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) to occur.
The recommended starting dose is 0.4–0.8 g/kg given once followed by at least 0.2g/kg given every 3–4 weeks.
The dose required to achieve a trough level of IgG 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 3–4 weeks. IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.
Replacement therapy in secondary immunodeficiencies (as defined in "Indications")
The recommended dose is 0.2–0.4 g/kg every 3-4 weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection.
Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.
Immunomodulation in:
Primary immune thrombocytopenia
There are two alternative treatment schedules:
• 0.8–1 g/kg given on day 1; this dose may be repeated once within 3 days.
• 0.4 g/kg given daily for 2–5 days. The treatment can be repeated, if relapse occurs.
Guillain Barré syndrome
0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).
Kawasaki Disease
2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.
If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease. The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of infusions
Replacement therapy:		
Primary immunodeficiency syndromes	Starting dose: 0.4 – 0.8 g/kg Maintenance dose: 0.2 – 0.8 g/kg	every 3 – 4 weeks
Secondary Immunodeficiencies (as defined in "Indications")	0.2 – 0.4 g/kg	every 3 – 4 weeks
Immunomodulation:		
Primary immune thrombocytopenia	0.8 – 1g/kg Or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2 – 5 days
Guillain Barré syndrome	0.4 g /kg/d	for 5 days
Kawasaki disease	2 g/kg	in one dose in association with acetylsalicylic acid

Method of administration
For Intravenous use. Human normal immunoglobulin should be infused intravenously at an initial rate of 0.01-0.02 mL/kg/min for 30 minutes. See "Adverse Reactions". In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.06 mL/kg/min.

[OVERDOSE]
Overdoses may lead to fluid overload and hyper viscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.

[PHARMACODYNAMIC PROPERTIES]
Pharmacodynamic group : immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code : J06BA02. Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin 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.
The mechanism of action in indications other than replacement therapy is not fully elucidated.

[PHARMACOKINETIC PROPERTIES]
Human normal immunoglobulin 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.
IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

[WARNING]
Thrombotic and thromboembolic events, including myocardial infarction, cerebral vascular accident, deep vein thrombosis and pulmonary embolism have been reported in association with immunoglobulins. (see "Adverse Reactions").
Patients at risk may include those with obesity, hypertension, history of atherosclerosis, history of vascular disease or thrombotic episodes, multiple cardiovascular risk factors, advanced age, impaired cardiac output, diabetes mellitus, acquired or inherited thrombophilic disorders and/or known or suspected hyperviscosity, hypercoagulable disorders, use of oestrogens, indwelling central vascular catheters, severe hypovolaemia and prolonged periods of immobilisation.
The potential risks and benefits of immunoglobulins should be weighed against those of alternative therapies for all patients for whom immunoglobulins administration is being considered. Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. The drug product should be administered at the minimum dose available and at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronaemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity assessed.

[CONTRAINDICATION]
1) Patients with history of hypersensitivity to the ingredients of this medicine
2) Patients with history of shock from the ingredients of this medicine
3) Patients with hypersensitivity to immunoglobulins (especially patients with anti-IgA antibodies)

[PRECAUTIONS]
1) Patients with immunoglobulin A (IgA) deficiency (Hypersensitivity may occur in patients with anti-IgA antibody.)
2) Patients with renal disorder (There is a risk of this drug aggravating renal function.)
3) Patients with haemolytic or haemorragic anaemia (There is a possibility of human parvovirus B19 infection. In case of infection, acute systemic responses may occur along with fever and severe acute anaemia.)
4) Patients who are immunodeficient or immunocompromised (There is a possibility of human parvovirus B19 infection. In case of infection, prolonged anaemia may occur.)
5) Patients with brain/cardiovascular disorder with the history of such diseases (For the elderly or those who are having ischaemic disease, cardiovascular disease, cerebral apoplexy, vascular lesion or the history of those diseases, the medication could cause thrombosis of cerebral infarction or myocardial infarction by increased blood viscosity from high dose.)
6) Patients with high possibility of thromboembolism (For the elderly or those who are having ischaemic disease, cardiovascular disease, cerebral apoplexy, vascular lesion or the history of those diseases, the medication could cause thromboembolism such as cerebral infarction or myocardial infarction by increased blood viscosity from high dose.)
7) Patients with decreased heart function (High dose could cause onset or worsening of heart failure.)

[ADVERSE REACTIONS]
1) Infusion reaction: Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) 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.
Adverse reactions may occur more frequently
- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion
- in patients with an untreated infection or underlying chronic inflammation

2) Hypersensitivity: Hypersensitivity reactions are rare.
Anaphylaxis can develop in patients
- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.
3) Thromboembolism: There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients, patients with diseases which increase blood viscosity). In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.
4) Acute renal failure: 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, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65. Renal parameters should be assessed prior to infusion of IVIG, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered. While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain these excipients may be considered. Immunoglobulins SG Injection 5% contains maltose. (See "Composition" above). Immunoglobulins SG Injection 5% does not contain sucrose or glucose.
5) Aseptic meningitis syndrome (AMS): Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment. Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

6) Haemolytic anaemia: IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis.
7) Neutropenia/Leukopenia: A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIgs. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.
8) Transfusion related acute lung injury (TRALI): In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Summary of the safety profile

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass:
- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

Tabulated list of adverse reactions

The table presented below is according the MedDRA System Organ Class (SOC) and Preferred Term Level (PT).
Frequencies were evaluated according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1
Frequency of Adverse Reaction (ADRs) in clinical study with Immunoglobulins SG Injection

MedDRA System Organ Class (SOC)	Adverse Drug Reaction	Frequency
Nervous system disorders	Headache	Very common
	Dizziness	Common
General disorders and administration site conditions	Pyrexia	Common
	Fatigue	Common
	Sensation of heat	Common
Skin and subcutaneous tissue disorders	Urticaria	Common
	Pruritus	Common
	Dermatitis acneiform	Common
Musculoskeletal and connective tissue disorders	Myalgia	Very common
Investigations	Neutrophil count decreased	Common
	C-reactive protein increased	Common
	Weight increased	Common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	Common
Gastrointestinal disorders	Nausea	Common
Metabolism and nutrition disorders	Decreased appetite	Common

The Post-Marketing Surveillance was conducted for 4 years in Korea. A total of 675 patients were enrolled, who were diagnosed as one of the following indications: agammaglobulinemia, hypogammaglobinemia, idiopathic thrombocytopenic purpura, Guillain-Barre syndrome, Kawasaki disease or combination therapy with antibiotics in severe infectious disease.

The summary of adverse events (AEs) and adverse drug reactions (ADRs) reported during the study period are presented in the tables below. A total of 444 cases of AEs occurred to 34 (94.44%) out of 36 subjects after receiving Liv-Gamma SN Injection. Among the AEs, 436 cases of ADRs, for which the relationship to Liv-Gamma SN Injection could not be ruled out, occurred to 33 subjects (91.67%).

The following table shows an overview of the ADRs observed in the post-marketing surveillance study categorized according the MedDRA System Organ Class (SOC), Preferred Term Level (PT) and frequency.

Frequencies were evaluated according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 2
Frequency of Adverse Reaction (ADRs) in Post-Marketing Surveillance with Immunoglobulins SG Injection

MedDRA System Organ Class (SOC)	Adverse Drug Reaction	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
General disorders and administration site conditions	Pyrexia	Uncommon
Haepatobiliary disorders	Hepatic function abnormal	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
Nervous system disorders	Somnolence	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Uncommon

[GENERAL PRECAUTIONS]
1) Careful administration and close monitoring are required as serious adverse event such as shock may be observed during continuous administration or repeated administration with intervals. In particular, when treating children or adolescents, caution should be exercised in infusion rate and patients must be closely monitored.
2) It must be noted that the treatment of idiopathic thrombocytopenic purpura by this medicine is not a causal treatment but a symptomatic treatment.
3) It should be noted that spontaneous remission has been observed in most cases of acute idiopathic thrombocytopenic purpura in children.
4) The patients should be closely monitored since the possibility of infection cannot be ruled out as it is difficult to completely inactivate or eliminate human Parvovirus B19 in the plasma derivatives produced under the current manufacturing process.
5) Along with the necessity of this drug in the treatment of the disease, patients should be informed that the risk of infection derived from human blood cannot be excluded completely, although certain safety measures are applied in the production process of this drug in order to prevent infection.
6) Since the drug contains anti-A and B blood type antibodies, if high dose is administered to patients of blood type A, B and AB, it could cause haemolytic anaemia.
7) Additional administration to patients with Kawasaki disease should be only delivered when it is considered necessary, such as when the administration has had a little effect (due to continuous fever, etc.). (Safety and efficacy of additional administration of this drug has not yet been confirmed.)
8) For severe infection cases, administration of this drug in combination with antibiotics must be targeted for patients with severe infections who cannot receive satisfactory results with antimicrobial chemotherapy.
9) Intravenous infusion of immunoglobulin is reported to be relevant to renal dysfunction, renal failure, osmotic nephrosis, death, etc.
10) The patient should be aware of the risk of thrombosis, discuss with the physician about the risk factor or concerns, and when thrombotic symptoms occur during or after administration, this should be discussed with the physician. Thrombotic symptoms include pain and swelling in arms and legs accompanied with slight fever, discoloration of arms and legs, cryptogenic dyspnoea, worsened chest pain or discomfort during deep breathing, cryptogenic rapid pulse, chest pain, numbness or weakness on one side of body, etc.
11) Healthcare professionals prescribing this drug should be aware of the risk of thrombosis and should discuss thrombosis with the patient, should monitor carefully during and after administration and should recommend the patient to inform signs and symptoms.
12) Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) may be related to infusion rate. The recommended infusion rate given under [DOSAGE AND ADMINISTRATION] must be closely followed. Patients must be closely monitored for any symptoms throughout the infusion period.

[DRUG INTERACTIONS]
1) 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 medicinal 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.
2) Loop diuretics: Avoidance of concomitant use of loop diuretics
3) Interference with serological testing: After the administration of 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 antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).
4) Paediatric population: The listed interactions apply both to adults and children.

[INCOMPATIBILITIES]
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.

[FERTILITY, PREGNANCY AND LACTATION]
1) Pregnancy: The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are expected.
2) Breast-feeding: Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.
3) Fertility: Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

[PAEDIATRIC USE]
The safety of administration to low-birth weight infants and newborns has not been established.

[GERIATRIC USE]
1) Since the physiological function of the elderly is generally decreased, particular attention regarding the condition should be paid when treating the elderly.
2) Since the elderly with cerebrovascular or cardiovascular disorder or the history of such disorder has a risk of thromboembolism, the condition of the patient should be observed and administered with caution.

[EFFECT ON CLINICAL EXAMINATION]
Antibodies against pathogens or its substances of diverse infections are included, and those antibodies could be detected temporarily after administration. So clinical diagnosis should be made with caution.

[ATTENTION ON ADMINISTRATION]
1) This medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.
2) Since a rapid infusion could lower the blood pressure, intravenous drip infusion is recommended. In case of direct intravenous injection, infusion rate should be slowed. (Attention should be paid to patients with hypo- and agammaglobulinemia.)
3) Do not administer products containing insoluble matters or turbid products.
4) The drug should be used immediately after opening within an hour. Do not use the remaining volume after administration as the remaining volume could be contaminated by bacteria. (This drug is a protein solution suitable for bacterial growth with no preservatives.)
5) Do not use those that were frozen.

[STORAGE AND HANDLING]
1) There is a risk of rubber particle being mixed in the drug solution if the needle is injected to the rubber stopper in a lean or twisted position, and therefore the needle should be injected to the rubber stopper perpendicularly and slowly. If a rubber stopper particle is mixed to the drug solution, it should not be used.
2) Store at 2-8℃. Do not freeze.

[OTHERS]
There are reports of aseptic meningitis when administered in a large volume to children with idiopathic thrombocytopenic purpura.

[PACKING UNIT] Each vial contains
・2.5 g/50 mL of human normal immunoglobulin ・3.0 g/60 mL of human normal immunoglobulin
・5.0 g/100 mL of human normal immunoglobulin ・10.0g/200 mL of human normal immunoglobulin
Not all presentations may be available locally.

[SHELF-LIFE] 24 months from the manufacturing date.

[STORAGE CONDITION] Keep the vial in the outer carton in order to protect from light. Store at 2-8℃. Do not freeze.

SINXXXXP

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