EUGAMMA SN 10% INJ.

1. Name of the medicinal product

Eugamma SN 10% inj.

2. Qualitative and quantitative composition

Each 1 mL contains:
- Human Normal Immunoglobulin G 100 mg

**The total limit of Immunoglobulin A not more than 0.1 mg*

For the full list of excipients see section 6.1

3. Pharmaceutical form

Solution for Injection, colorless or pale yellow, clear or opalescent liquid

4. Clinical particulars

4.1 Therapeutic indications

1) A-/Hypo-gammaglobulinemia
2) Combined therapy with antibiotics in severe bacterial or viral infections
3) Idiopathic Thrombocytopenic Purpura (In the case where other medicinal products are not effective and patients show apparent hemorrhage and patients need temporary control of hemostasis such as surgeon treatments or childbirth etc.)
4) Guillain-Barre Syndrome (Acute idiopathic polyneuritis)
5) Kawasaki Disease (To prevent the disease of coronary artery complication)

4.2 Posology and method of administration

4.2.1 Recommended dose

1) A-/Hypo-gammaglobulinemia
   The usual dosage for adults is 200 – 600 mg/kg by an intravenous drip infusion or an intravenous bolus infusion every 3 – 4 weeks.
2) Combined therapy with antibiotics in severe bacterial or viral infections
   The usual dosage for adults and children is 2,500 – 5,000 mg and 50 – 150 mg/kg respectively by an intravenous drip infusion or an intravenous bolus infusion.
3) Idiopathic Thrombocytopenic Purpura (ITP)
   The usual dosage for the treatment of acute or chronic ITP is 1,000 mg/kg daily given for 2 consecutive days. Discontinue if an adequate response does not occur.
4) Guillain-Barre Syndrome
   The usual dosage is 400 mg/kg once a day for 5 consecutive days.
5) Kawasaki Disease
   The usual dosage is 400 mg/kg daily given for 5 consecutive days (approximately) or 2,000 mg/kg daily by an intravenous drip infusion. It is recommended that the administration of Eugamma SN 10% Inj. starts within 7 days from the onset of Kawasaki Disease. For the single infusion with 2,000 mg/kg injection, infusion rate follows Infusion rate as the criteria, Eugamma SN 10% Inj. is injected with an intravenous drip infusion method over 12 hours.

<u>Dosage in special population</u>

- Elders: N/A
- Renal Impairment Patients: N/A
- Hepatic Impairment Patients: N/A

4.2.2 Mode of Administration

Intravenous Infusion or Intravenous bolus

Infusion rate

The first dose should be infused at an initial rate of 0.01 – 0.02 mL/kg/min (for example, infusion rate will be 0.6 – 1.2 mL/min for the 60kg subject) for 30 minutes. After 30 minutes, the infusion rate can be gradually increased to 0.06 mL/kg/min if well tolerated. If any symptoms occur from increasing infusion rate, the infusion rate should be decreased or discontinued until symptoms subside.

4.3 Contraindications

1) Patients with history of hypersensitivity to ingredients of Immune Globulin Intravenous (IVIG) product

2) Patient with history of shock to ingredients of IVIG product

4.4 Special warnings and precautions for use.

4.4.1 Special warnings

1) Eugamma SN 10% Inj., manufactured from human plasma, has the potential to transmit hepatitis viruses or other transmissible agents (Theoretically, CJD) which can cause infection. The risk of virus infection cannot be entirely eliminated. Accordingly, patients with hemophilia or immunodeficiency are recommended to be appropriately vaccinated (Hepatitis A vaccine, etc.), and the attending physician should monitor patients regularly to check any sign of virus infection.

   Since Eugamma SN 10% Inj. has potential risks as described above, the patient should be fully informed at the time of administration and should only use the minimum necessary after careful consideration of the therapeutic need.

2) The risk of thrombosis by administration of this product cannot be entirely eliminated. Thrombosis may occur regardless of the route of administration and in the absence of known risk factors (advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors).

   For patients at risk of thrombosis, administer at the minimum concentration possible and at the minimum rate of infusion practicable. Also ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

4.4.2 Special precautions

1) Patients with IgA deficiency (Eugamma SN 10% Inj. may cause anaphylaxis to patients who have anti-IgA)

2) Patients with renal disorder (Renal function may deteriorate.)

3) Patients with hemolytic anemia or anemia from blood loss (Human parvovirus B19 infection may occur. In case of B19 infection, acute systemic symptoms with fever and severe anemia may occur.)

4) Patients with immunological incompetence or immunodeficiency (Human parvovirus B19 infection may occur. In case of infection, continuous anemia may occur.)

5) Patients with cerebrovascular and cardiovascular disorders or case history thereof for example, (Elderly patients with ischemic disease, cardiovascular disorder, cerebrovascular disorder; or patients with cerebrovascular and cardiovascular disorders or case history thereof: a large bolus administration can cause thrombosis or embolism such as cerebral infarction, a myocardial infarction, etc., due to blood viscosity increase.)

6) Patients with a high risk of thrombosis or embolism (Thrombosis or embolism may occur due to an increase of blood viscosity due to large bolus administration)

7) Patients with low heart function (A large bolus administration may cause heart failure or deterioration of heart condition administration)

4.4.3 General cautions

1) In the case of successive or interval administration, shock or severe abnormal reactions may occur. Accordingly, administration should be done with caution, and catamnesis also should be carefully observed. Especially for children, special caution should be taken for the rate of administration and catamnesis.

2) Administration of Eugamma SN 10% Inj. for the treatment of Idiopathic Thrombocytopenic Purpura is for symptomatic therapy, not causal treatment.

3) In the case of Idiopathic Thrombocytopenic Purpura for children, spontaneous remission should be considered.

4) In the present plasma fractionation process, it is difficult to inactivate or remove human parvovirus B19 etc. completely. Accordingly, possibilities of infection cannot be disregarded, and special caution should be taken for catamnesis.

5) Even though a safety plan for the prevention of the spread of infection is prepared, the risk of infection cannot be entirely disregarded since Eugamma SN Inj. originates from human blood. This risk should be explained to patients.

6) Since Eugamma SN 10% Inj. contains anti-A and anti-B, hemolytic anemia may occur when a large bolus is administered to patients with blood type A, B or AB.

7) Additional administration to patients with Kawasaki Disease should be conducted when additional administration is clearly necessary such as the effectiveness of Eugamma SN 10% Inj. is insufficient for symptomatic remission (e.g. Continuation of fever). (Safety and efficacy for additional administration has not been established)

8) In the case of combined therapy with antibiotics in severe infections, Eugamma SN Inj. should be used for patients who show insufficient response to proper antimicrobial chemotherapy.

9) There have been published reports that immunoglobulin intravenous injection is related to renal dysfunction, renal failure, osmotic nephrosis, death and etc.

10) Patients should be aware of the risk for thrombosis and discuss with their healthcare professionals and contact them if any signs or symptoms of thrombosis during or after receiving this product develop. Signs or symptoms of thrombosis may include pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens

on deep breathing, unexplained rapid pulse, chest pain and numbness or weakness on one side of the body.

11) Healthcare professionals should be aware of the risk for thrombosis with human normal immunoglobulin products and discuss with their patients the risk of thrombosis associated with this product. Monitor patients carefully for signs and symptoms of thrombosis both at the time of infusion and after infusion and encourage patients to report any signs or symptoms.

4.5 Interaction with other medicinal products and others forms of reaction

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines (Measles, Mumps, Rubella and Varicella vaccine etc.). There is a possibility that live vaccines do not work for the patients who were treated with Eugamma SN 10% Inj. Therefore, vaccination should be delayed for more than 3 months after administration. If Eugamma SN 10% Inj. is administered within 14 days after vaccination, re- vaccination should be taken after more than 3 months post Eugamma SN 10% Inj. administration. After a large bolus (more than 200 mg/kg) administration for the ITP and Kawasaki Disease, use of live vaccines should be delayed more than 6 months (In case of low risk of measles infection, measles vaccination should be delayed more than 11 months).

4.6 Pregnancy and lactation

Safety for pregnant women has not been established. The possibility of parvovirus B-19 infection cannot be excluded from the administration of Eugamma SN Inj. In case of parvovirus B-19 infection, fetal disturbances (Abortion, Hydrops fetalis, Fetal death) may occur. **Eugamma SN 10% Inj.** should be given to a pregnant woman only if the expected benefit justifies the possible risk.

4.7 Effects on ability to drive and use machines

Some of the effects mentioned under section '4.8 Undesirable Effects' may affect the ability to drive or use machines.

4.8 Undesirable effects

1) Shock
Symptoms of shock may occur occasionally. If dyspnea, wheeze, chest discomfort, drop in blood pressure or weak pulse is watched, administration should be discontinued, and 0.1 – 0.5 mL epinephrine (1:1,000) or the administration of cortisone should be considered.

2) Circulatory
Rapid infusion may result in a drop in blood pressure. (Caution should be taken to patients with A-/Hypo-gammaglobulinemia.)

3) Liver
Jaundice or hepatic impairment with markedly elevated ALT/AST may occur. The patient should be carefully monitored. If there are abnormal findings proper treatment should be taken.

4) Kidney
Acute renal failure has been reported with the use of immunoglobulin products. The patient should be sufficiently hydrated before dosing and should be thoroughly monitored for decreased urine output, increased creatinine, and increased BUN. If any of these occur, the therapy should be stopped, and appropriate treatment

should be provided. The administration dosage and rate should be lowered (as low as possible) for patients at high risk for acute renal failure.

5) Central Nervous System
Sterile meningitis (headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting) may occur due to a high dose administration, in which case, the therapy should be stopped, and appropriate treatment should be taken

6) Blood
Because a decrease in platelets may occur with the administration of Eugamma SN 10% Inj., recipients should be monitored. If this symptom occurs, proper treatment should be taken.

7) Other possible undesirable effects
Drowsiness, chill, chest pain, back pain, gluteal pain and anxiety etc.

8) Results of the post-marketing surveillance in South Korea
In accordance with the results of post-marketing surveillance conducted in Korea on 615 patients for 4 years, the incidence rate of adverse events was 17.72% (109/615 patients, total 225 cases) regardless of casual relationship. Among these, serious adverse drug reactions and unexpected adverse drug reactions for which causality cannot be excluded are listed in the table below according to their frequency of occurrence.

		Severe ADR	Unexpected ADR
		0.33% (2/615 patients, 2 cases)	1.46% (9/615 patients, 10 cases)
Sometime (0.1% - 5%)	General disorders and administration site conditions	Pyrexia	-
	Infections and infestations	-	Herpes zoster
	Metabolism and nutrition disorders	-	Hyperphosphatemia
	Skin and subcutaneous tissue disorders	-	Urticaria, pruritus
	Investigations	–	Weight increased; blood pressure increased
	Vascular disorders	-	Hypertension, cyanosis
	Nervous system disorders	-	dizziness

Post-marketing surveillance results of adverse reactions in South Korea
As a result of analysis and evaluation of signals based on the reported data of adverse events during post-marketing use (1989 – Sep. 30, 2021) including adverse events of post-marketing surveillance the following adverse events have been identified. However, this does not mean that a causal relationship has been established between the ingredient and the following adverse events.

- Occurs during or immediately after infusion: pyrexia, tachycardia, and blood pressure increased.

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

4.10 Special populations

Special population on Pediatric use
Safety for low-birth-weight infants and neonates has not been established. Aseptic meningitis has been reported following large volume administration of immunoglobulin products for pediatric subjects with Idiopathic Thrombocytopenic Purpura and etc.

Special population on Geriatric use
Since elderly patients generally have low physiological function, Eugamma SN 10% Inj. should be administered with special care.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
- **immune sera and immunoglobulins:** immunoglobulins, normal human, for intravascular administration
- **ATC code:** J06BA02

Mechanism of action
Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious microorganisms.

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 IgG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

The mechanism of action in indications other than replacement therapy is not fully elucidated but includes immunomodulatory effects.

5.2 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 extra-vascular compartments.

The half-life may vary from patient to patient, in particular in primary immunodeficiency. IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data

The sponsor has conducted both non-Good Laboratory Practice (GLP) and GLP nonclinical pharmacology studies to elucidate the characteristics of Eugamma SN 10% Inj. The IgG in **Eugamma SN 10% Inj.** provides antibody activities against a broad spectrum of infectious microorganisms. The three efficacy studies of Eugamma SN 10% Inj. were evaluated in a primary humoral immunodeficiency (PHID) model using *Streptococcus pneumoniae* (*S. pneumoniae*) and *Klebsiella pneumoniae* (*K. pneumoniae*) and antibody-induced idiopathic thrombocytopenic purpura (ITP) model. The results were showed equal antibacterial effect and thrombocytopenia-amelioratory effect compared to marketed product.

Eugamma SN 10% Inj. tested in three safety pharmacology studies. In a cardiovascular study in rats, Eugamma SN 10% Inj. did not affect the blood pressure and heart rate following a single intravenous administration at a dose of up to 2,000 mg/kg. The results of a central nervous study in ICR mice showed no related effects on body temperature and general behavior following a single dose administration of up to 2,000 mg/kg. In the third study, which measured respiration rate, tidal volume and minute volume, there were no significant differences in these parameters in any Eugamma SN 10% Inj. groups (2,000 mg/kg or less) compared to the negative control group (physiological saline solution).

6. Pharmaceutical particulars

6.1 List of excipients

Glycine, water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store at 1 – 25°C in hermetic container.

6.5 Nature and contents of container

10, 25, 50, 100 and 200 mL of solution in vial (Type I glass) with a rubber stopper (chlorobutyl rubber) vial

6.6 Special precautions for disposal and other handling

1) Avoid mixing with other medicinal products except for 5% Dextrose injection (Do not mix with normal saline and other immunoglobulin products)

2) Since hypotension may occur if infusion rate is fast, the intravenous drip infusion is appropriate. In the case of intravenous bolus infusion, the infusion rate should be as slow as possible. And patients with A-/Hypo-gammaglobulinemia should be observed closely.

3) If particulate matter is observed, or color is not clear, the product should be discarded.

4) Eugamma SN 10% Inj. should be used within 1 hour after the container is opened. Do not use the remaining solution due to the concern of microbial contamination. (Because proteins in Eugamma SN 10% Inj. are an environment in which microorganisms can grow easily as it does not contain preservatives.)

5) Do not use if Eugamma SN 10% Inj. was ever frozen.

6) When a needle is inserted through the rubber stopper, the needle should be inserted vertically and slowly. If a needle is inserted in a tilted or twisted direction, rubber fragments may be mixed with medicinal products. If there are any rubber

fragments, discard the product.

7) Store at 1-25˚C without freezing.

7. Marketing authorization holder

S. Charoen Bhaesaj Trading Co., Ltd.
711,713-715-717 Mahachai Road, Wangburapapirom,
Pranakorn, Bangkok, THAILAND, 10200
Tel: (+66) 2621 1301, Fax: (+66) 2621 1310

8. Marketing authorization number

1C XXXX/YY (B)

9. Date of first authorization/renewal of the authorization

YYYY.MM.DD

10. Date of revision text

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