SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

1.1 Product name

Gamma I.V. – 5.0

Normal Immunoglobulin for Intravenous use B.P.

1.2 Strength

Each vial contains 0.05gm/ml of human normal immunoglobulin

1.3 Pharmaceutical dosage form

Injection

2. Qualitative and Quantitative compositions

Name of the component	Specification	Quantity / mL	Justification for use of Ingredient
Immunoglobulin G	I.H.	50 mg	Active Ingredient
Maltose	I.H.	100 mg	Stabilizer
Glycine	B.P.	0.375 mg	Stabilizer
Hydrochloric acid*	B.P.	q	pH adjustment
Water for Injection	B.P.	q	Vehicle

Note: B.P. : British Pharmacopoeia
I.H. : In-house
q.s.: quantity sufficient

3. Pharmaceutical form

Injection

4. Clinical particulars

4.1 Therapeutic Indications

Gamma I.V. is indicated in the treatment of primary immunodeficiency states in which severe impairment of antibody forming capacity has been shown. Gamma I.V. is especially useful when high levels or rapid elevations of circulating antibodies are desired or when intramuscular injections are contraindicatory.

Gamma I.V. is indicated for following conditions:

1. Primary Immunodeficiency (PID)
2. Kawasaki syndrome
3. Idiopathic Thrombocytopenic Purpura (ITP)
4. Bone Marrow Transplantation
5. Chronic B-cell Lymphocytic Leukemia
6. Pediatric HIV-1 Infection
7. Guillain-Barre syndrome (GBS)

4.2 Posology and method of administration

In general it is recommended that Gamma I.V. be administered by itself on an initial rate of 0.01 to 0.02 ml/kg body weight/minute for 30 minutes, if well tolerated the rate may be gradually increased to a maximum of 0.08 ml/kg body weight/minute.

Gamma I.V. is recommended to be given by a separate line, by itself without mixing with other intravenous fluids or medications the patients might be receiving. Gamma I.V. is not compatible with saline. The dilution if required, Gamma I.V. may be diluted with 5% Dextrose in water.

The recommended dosages for the specific indications are as follows:

Primary Immunodeficiency - for Prophylaxis -

100 to 200mg/kg body weight (2 - 4 ml/kg) approximately once a month. The dosage may be given more frequently or increased to as high as 400mg/kg body weight if the clinical response is inadequate.

Kawasaki syndrome - Dose of 400mg/kg body weight daily for 4 days or alternatively a single dose of 2gm/kg. Patients should receive treatment with acetylsalicylic acid concomitantly.

Idiopathic Thrombocytopenic Purpura - (ITP) -

400mg/kg body weight daily for 5 days. Alternatively 1000mg/kg body weight daily for one day or two consecutive days. Subsequently maintenance dose of 400mg - 1000mg/kg weight as single infusion intermittently.

Bone Marrow Transplantation -

500mg/kg (10 ml/kg) body weight beginning on - 7 and 2 pretransplant and then weekly through 90 days of post-transplant.

Chronic B-cell Lymphocytic Leukemia - 400mg/kg every 3 weeks

Pediatric HIV-1 Infection - 400mg/kg every 28 days

Guillain - Barre Syndrome - 400mg/kg per day for 5 days

Route of Administration: Intravenous

4.3 Contra-indications

Gamma I.V. is contraindicated in individuals who Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Individuals with selective IgA deficiencies should not receive Gamma I.V. since these individuals may experience severe reactions to the IgA which may be present.

4.4 Special warning and precautions for use

Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate given under section 4.2 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 case of high rate of infusion

− 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.

Potential complications can often be avoided by ensuring that patients:

− are not sensitive to human normal immunoglobulin by initially injecting the product slowly (1.4 ml/kg/h corresponding to 0.023 ml/kg/min),

− 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.

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 adverse reaction.

In case of shock, standard medical treatment for shock should be implemented. 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

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

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.

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.

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 years.

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 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.

In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

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. 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.

Interference with serological testing

After injection 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).

Transmissible agents

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 human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus 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 Gamma IV is administered to a patient, the name and batch number of the product are recorded to maintain a link between the patient and the batch of the product.

Paediatric population

The special warnings and precautions for use mentioned for the adults should also be considered for the paediatric population.

Excipients

Maltose is present as an excipients may result in false elevated glucose or mask true hypoglycaemia.

4.5 Interaction with other drugs, other forms of interactions

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.

Interference with serological testing

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

4.6 Use in pregnancy and lactation

Animal reproduction studies have not been conducted with Gamma I.V. Hence it is not known whether Gamma I.V. can cause fetal harm when administered to pregnant woman or can affect the reproduction capacity.

4.7 Effects on ability to drive and operate machine

No effect on ability to drive or use machines have been observed.

4.8 Undesirable effects

Primary Humoral Immunodeficiency:

In patients with immunodeficiency syndrome receiving Gamma I.V. at a montly dose of 400 mg / kg body weight, the ractions reported have been malaise, feeling of faintness, fever, chills, headache, nausea, vomiting, chest tightness, dyspnea and chest, back or hip pain. Mild erythema at the infusion site has also been reported in some cases.

Idiopathic Thrombocytopenic Purpura: (ITP)

In the treatment of adult and padeatric patients with ITP at a dose of 400 mg/kg body weight, the systemic reactions were observed only in less than 3% of the patients. The other symptoms which were all mild and transient include chest tightness, a sense of tachycardia and a burning sensation in head.

At a dose of 100 mg / kg body weight either as a single dose or as two doses on consecutive days in the treatment of adult and paediatric patients with ITP. Adverse reactions have been noted only in less than 10% of the patients.

Bone Marrow Transplantation:

At a dose of 500 mg/kg body weight 7 days and two days before transplant and weekly through 90 days of post-transplant, adverse reactions were reported in less than 7% of the patients. All reactions were classified as mild which include headache, flushing, fever and slight back discomfort.

General:

A reaction to Gamma I.V. is related to the rate of infusion. Very rarely an anaphylactoid reactions may occur in patients with no prior history of severe allergic reactions to either intramuscular or intravenous immunoglobulin.

4.9 Overdoses

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

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic 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, but includes immunomodulatory effects.

Primary Humoral Immunodeficiency:

Gamma I.V. supplies a broad spectrum of opsonic and neutralizing lgG antibodies for the prevention or attenuation of wide variety of infectious diseases. As Gamma I.V. is administered intravenously, essentially 100% of the infused lgG antibodies are immediately available in the recipient circulation. 30% of the infused lgG disappeared from the circulation in first 24 hours.

A further decline to about 40% of the peak level is observed during first week. The in-vivo half-life of Gamma I.V. equals or exceeds the three week half-life reported in the literature.

Idiopathic Thrombocytopenic Purpura: (ITP)

Gamma I.V. has been shown to be effective in ITP. The mechanism of action has not been fully elucidated.

Bone Marrow Transplantation:

Gamma I.V. has been shown to be effective in bone marrow transplant patients 20 years of age in the first 100 days post - transplant for the prevention of systemic and local infections, interstitial pneumonia of infectious and idiopathic etiologies. In patients with limited or compromised acid-base compensatory mechanisms, consideration should be given to the effect of the additional acid load Gamma I.V. may present.

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 extravascular compartments.

Human normal immunoglobulin has a half-life of about *(insert product specific half-life)* days. This half-life may vary from patient to patient, in primary immunodeficiency.

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

6. Pharmaceutical particulars

6.1 List of Excipients

Excipients	Pharmacopoeial claim
Maltose	I.H.
Glycine	B.P.
Hydrochloric acid*	B.P.
Water for Injection	B.P.

B.P.: British Pharmacopoeia
I.H.: In-house

6.2 Incompatibilities

Not Applicable

6.3 Shelf-life

24 months from the date of manufacturing.

6.4 Special precaution for storage:

Store the product at 2^0C - 8^0C. Protect from light. Do not freeze

6.5 Nature and contents of container:

Gamma I.V. – 5.0 (Normal Immunoglobulin for Intravenous use B.P.) is supplied as a single dose in a 100 ml USP Type – I, moulded flint glass vial.

7. Marketing authorization holder :

Bharat Serums & Vaccines Ltd.
17th Floor, Hoechst House,
Nariman Point,
Mumbai – 400 021
India.

8. Marketing authorization number:

Not Applicable

9. Date of first authorization / renewal of authorization:

Not Applicable

10. Date of revision of the text:

Not Applicable