130 mm

270 mm

For the use of a Registered Medical Practitioner only.

Human Normal Immunoglobulin for Intravenous Use I.P. 5%, Solution (Xtra Purified)
GLOBUCEL® XP
(5g/100ml)
ग्लोबुसेल एक्सपी
Manufactured from human plasma
For Intravenous Use Only

GENERIC NAME
Human Normal Immunoglobulin for Intravenous Use I.P. 5%, Solution

QUALITATIVE AND QUANTITATIVE COMPOSITION
Concentration Available 5%
Pack size 100 ml
Each vial contains:
Total Protein.....50 g/L
Immunoglobulin G.....≥ 95%
Glycine (as stabilizer).....22.5 g/L
IgA Content.....≤80 mg/L
IgG subclass.....Normal Distribution
Water for Injection .....q.s.

DOSAGE FORM AND STRENGTH
Human normal immunoglobulin solution is for intravenous (I.V.) use only.
It is supplied as 100 ml (5 g) vial.

CLINICAL PARTICULARS
THERAPEUTIC INDICATION
Immunoglobulin preparations are indicated in several clinical conditions. An approved list of clinical conditions where IVIG is indicated is as under:

Primary Immunodeficiency (PID) Syndromes
Replacement therapy to promote passive immunity: the following PID syndromes can be treated with intravenous replacement of IgG and are considered well established:
- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiency
- X-linked agammaglobulinaemia
- Wiskott-Aldrich syndrome
- Severe combined immunodeficiencies

IVIG may be preferred in patients who require an immediate or large increase in intravascular immunoglobulin concentrations, in patients with small muscle mass, and in patients with bleeding tendencies in whom Intramuscular (IM) injections are contraindicated.

Secondary Immunodeficiency (SID) Syndromes
IgG can also be used as replacement therapy in:
- Secondary hypogammaglobulinaemia in patients with B-cell chronic lymphocytic leukaemia (CLL) or multiple myeloma (MM) with recurrent infections.
- Paediatric HIV-I infection who have bacterial infections: HIV-infected infants and children with hypogammaglobulinaemia (IgG <400 mg/dL) should receive IVIG (400 mg/kg once every 2–4 weeks) to prevent serious bacterial infections.

Kawasaki Syndrome
IVIG is used in conjunction with aspirin therapy for initial treatment of the acute phase of Kawasaki disease.

Idiopathic Thrombocytopenic Purpura
IVIG is indicated for the treatment of acute or chronic (e.g., >6 months duration) idiopathic thrombocytopenic Purpura.

Allogenic Bone marrow transplantation (BMT)
In adults and children undergoing BMT, IVIG can be used to decrease the risk of infections (e.g., septicemia), interstitial pneumonia of infectious or idiopathic etiologies, and acute graft-versus-host disease.

Guillain-Barre syndrome
IVIG initiated within 2 weeks of symptom onset appears to be as effective as plasma exchange.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
IVIG may be used for the treatment of chronic inflammatory demyelinating polyneuropathy to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

POSOLOGY AND METHOD OF ADMINISTRATION
For intravenous use only.
- IVIG liquid should be inspected visually for particulate matter and discoloration prior to administration,
- IVIG liquid should be at room temperature during administration. Any bottle that has been opened should be used promptly.
- Prior to initiation of IVIG infusion, ensure that patients are adequately hydrated.
- In general, in patients receiving initial doses of IVIG or switching from one IVIG preparation to another, initiate the infusion rate at the lower end of the recommended range and increase to the maximum recommended rate only after the patient has tolerated several infusions at an intermediate infusion rate.
- If an adverse reaction occurs during the IVIG infusion, decrease the rate of infusion or stop the infusion until the reaction subsides.
- Irrespective of blood group, it can be transferred to all recipients.

Primary Immunodeficiency Syndrome
As there are significant differences in the half-life of IgG among patients with primary humoral immunodeficiencies, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The dose of IVIG liquid for replacement therapy in primary humoral immunodeficiency diseases is 300 to 600 mg/kg body weight (6-12 mL/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical responses.

Rate of Administration of IVIG 5%	mg/kg/min (mg/kg/hour)	mL/kg/min
First 30 min	0.5 (30)	0.01
Next 30 min	1.0 (60)	0.02
Next 30 min	2.0 (120)	0.04
Maximum	< 3.33 (<200)	<0.07

It is recommended that IVIG liquid be initially infused at infusion rates stated below,
For patients judged to be at risk for developing renal dysfunction or thromboembolic events, administer IVIG liquid at the minimum infusion rate practicable, not to exceed 0.07 mL/kg (3.3 mg/kg)/minute (200 mg/kg/hour). discontinue IVIG if renal function deteriorates.

Table: Dosage recommendation for human intravenous immunoglobulin

Indication	Dose
Replacement therapy in primary immunodeficiency syndromes	Starting dose: 0.3 - 0.6 g/kg followed every 3 -4 weeks adjusted to achieve desired trough serum IgG concentration and clinical response.
Replacement therapy in secondary immunodeficiency syndromes	0.2 - 0.4 g/kg, every 3 - 4 weeks adjusted to achieve desired trough serum IgG concentration and clinical response
Kawasaki syndrome	2 g/kg in one dose in association with acetylsalicylic acid or 1.6 - 2 g/kg in several doses for 2 - 5 days in association with acetylsalicylic acid
Idiopathic thrombocytopenic purpura	0.2- 0.4 g/kg for 5 days or 0.8 – 1 g.kg on day 1, possibly repeated once with in three days.
B-cell Chronic lymphocytic Leukemia	Recommended dose is 0.4 g/kg every 3 - 4 weeks.
Paediatric HIV-I infection	0.2 – 0.4 g/kg every 2 – 4 weeks.
Allogenic bone marrow transplantation: (1) Treatment of infection and prophylaxis of graft versus host disease (2) Persistent lack of antibody production	0.5 g/kg every week from day -7 up to three months after transplantation.Individualize dosage to maintain trough serum IgG concentrations exceeding 400–500 mg/dL; monitor trough serum IgG concentrations approximately every 2 weeks. 0.5 g/kg every month until antibody levels return to normal.
Guillain-Barre syndrome	0.4 g/kg /d for 5 days
Chronic inflammatory demyelinating polyneuropathy	Initially loading dose of 2 g/kg (40 mL/kg) given in divided doses over 2 to 4 consecutive day.Maintenance infusion of 1 g/kg (20 mL/kg) administered over 1 day or divided into two doses of 0.5 g/kg (10 mL/kg) given on 2 consecutive days, every three weeks.

USE IN SPECIAL POPULATION
Pregnancy
US-FDA Pregnancy category C.
Animal reproduction studies have not been conducted with intravenous immunoglobulin (IVIG). It is also not known whether intravenous immunoglobulin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Intravenous immunoglobulin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
Intravenous immunoglobulin has not been evaluated in nursing mothers.

Pediatric Use
Safety and efficacy of intravenous immunoglobulin have not been established in children under 2 years of age. No obvious differences observed between adults and pediatric subjects with respect to pharmacokinetics, efficacy and safety. No pediatric specific dose requirements were necessary to achieve the desired serum IgG levels.

Geriatric Use
Patients > 65 years of age may be at increased risk for developing certain adverse reactions such as thromboembolic events and acute renal failure (See Warnings and Precautions).

CONTRAINDICATIONS
IVIG is contraindicated in individuals who have had anaphylactic or severe systemic reactions to immunoglobulin or any ingredients in the formulation.
IVIG is contraindicated in individuals with selective IgA deficiency or IgA deficiency with antibodies against IgA.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Sensitivity
Severe hypersensitivity reactions, including anaphylaxis, reported rarely following administration of Intravenous Immunoglobulin (IVIG). If a severe hypersensitivity reaction occurs, discontinue immune globulin immediately and institute appropriate therapy as indicated. Patients known to have corn allergies should avoid using IVIG (See CONTRAINDICATIONS).

Infusion Reactions
There is a risk of reactions including fever, chills, nausea, and vomiting upon IV infusion. These reactions generally appear 30 minutes to 1 hour after initiation of the infusion and include flushing of the face, tightness in the chest, chills, fever, dizziness, nausea, vomiting, diaphoresis, and hypotension or hypertension. Closely monitor for adverse reactions throughout the infusion since these reactions may rarely lead to shock.

Acute renal failure
Renal dysfunction, acute renal failure, osmotic nephrosis, and death reported in patients receiving immune globulin. Patients at increased risk for acute renal failure include those with any degree of preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; those receiving concomitant nephrotoxic drugs; and/or those >65 years of age. To minimize risk of acute renal failure, ensure that patients are not volume depleted and are adequately hydrated prior to administration of IVIG. Always use lowest efective dosage at the minimum concentration available and at the minimum practicable rate of infusion, especially in patients at increased risk for acute renal failure. Assess urine output and renal function including blood urea nitrogen (BUN)/ serum creatinine, prior
to and at appropriate intervals during therapy with IVIG, especially in patients considered at increased risk for acute renal failure. If renal dysfunction occurs, consider discontinuing immune globulin therapy.

Thrombotic Effects
Thrombotic events (e.g., chest pain, MI, CHF, cerebral infarction, ischemic encephalopathy, severe headache requiring hospitalization, pulmonary embolism, retinal vein occlusion, peripheral venous thrombosis), including some fatalities, reported in patients receiving IVIG. IVIG-induced alterations of blood rheology (e.g., platelet activation, increased blood viscosity) and infusion-related hypertensive effects appear to contribute to the development of thrombotic complications. Patients with a history of atherosclerosis, multiple cardiovascular risk factors, hypertension, impaired cardiac output, cerebrovascular disease, coronary artery disease, coagulation or hypercoagulable disorders (e.g., factor V Leiden), prolonged periods of immobilization, advanced age, obesity, diabetes mellitus, acquired or inherited thrombotic disorder, previous thrombotic or thromboembolic event, or known or suspected hyperviscosity, and/or those receiving estrogen-containing products may be at increased risk.

Hemolysis
IVIG and immune globulin subcutaneous can contain blood group antibodies which may act as hemolysins and induce in vivo coating of RBCs with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.
Hemolytic anaemia also can develop subsequent to immune globulin therapy due to enhanced RBC sequestration and/or intravascular RBC destruction.

Transfusion-related Acute Lung Injury
Transfusion-related acute lung injury (noncardiogenic pulmonary edema) has been reported in patients receiving IVIG. Typically occurs within 1–6 hours after the infusion and is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Monitor patients receiving Human normal immunoglobulin solution for adverse pulmonary reactions. If transfusion-related acute lung injury is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in both the product and patient serum. Manage using oxygen therapy with adequate ventilatory support.

Aseptic Meningitis Syndrome
Aseptic meningitis syndrome reported infrequently in patients receiving immune globulin, especially at high doses (e.g., >1 g/kg) and/or by rapid IV infusion which should be rarely possible with Human normal immunoglobulin solution. Symptoms (e.g., severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, vomiting) may occur within several hours to 2 days following the administration.

Hyperproteinemia, Increased Viscosity, and Hyponatremia
Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IVIG. The hyponatremia is likely to be pseudohyponatremia, as demonstrated by decreased calculated serum osmolality or elevated osmolar gap.
If hyponatremia occurs, it is critical to distinguish true hyponatremia from pseudohyponatremia. Treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and may predispose to thromboembolic events.

Volume Overload
High-dose IVIG regimens (1 g/kg daily for 1–2 days) used for treatment of chronic ITP are not recommended in individuals with expanded fluid volumes or when fluid volume may be a concern.

DRUGS INTERACTIONS
It is recommended that intravenous immunoglobulin liquid be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with IVIG from other manufacturers.
Various passively transferred antibodies in immunoglobulin preparations can confound the results of serological testing.
Antibodies in intravenous immunoglobulin (IVIG) may interfere with the response to live viral vaccines, including measles, mumps, and rubella virus vaccine live (MMR) and varicella virus vaccine live. No evidence of interference with the immune response to influenza virus vaccine live intranasal, yellow fever virus vaccine live, typhoid vaccine live oral, rotavirus vaccine live oral, zoster vaccine live, or poliovirus vaccine live oral. However, caution should be exercised during use of above vaccine and physicians should follow the prescribing information of respective vaccine. Physicians should be informed of recent therapy with IVIGs, so that administration of live viral vaccines, if indicated, can be appropriately delayed 3 or more months from the time of IVIG administration. 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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No information on the ability to drive and use machines have been known.

UNDESIRABLE EFFECTS
Certain severe drug reactions may be related to the rate of infusion. Possible adverse reactions with human normal immunoglobulin solution are listed below.
The most common adverse reactions reported in ≥ 5% of clinical trial subjects occurring during or within 48 hours of an infusion were headache, nausea, chills, asthenia (fatigue), pyrexia, upper abdominal pain, diarrhea, back pain, hyperhidrosis, and flushing. In post-marketing surveillance, serious adverse reactions reported with intravenous immunoglobulin were anaphylaxis, acute renal failure, myocardial infarction, cerebral vascular accident, transient ischemic attack, deep vein thrombosis, pulmonary embolism, aseptic meningitis, acute hemolysis, and TRALI. Rare cases of transient cutaneous reactions (including cutaneous lupus erythematosus) have been observed.
The following adverse reactions have been identified during post-approval use of IVIG products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to IVIG products:

Blood and lymphatic system disorders: Leukopenia, haemolytic anaemia, pancytopenia, leukopenia, hemolysis
Immune system disorders: Hypersensitivity, anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, angioneurotic oedema, face oedema
Metabolic and nutritional disorders: Fluid overload
Psychiatric disorders: Agitation
Nervous system disorders: Headache, cerebrovascular accident, meningitis aseptic, migraine, dizziness, paraesthesia, coma, loss of consciousness, seizures, tremors
Cardiac disorder: Myocardial infarction, tachycardia, palpitations, cardiac arrest, thromboembolism
Vascular disorders: Hypotension, thrombosis, peripheral circulatory failure, hypertension , vascular collapse
Respiratory, thoracic and mediastinal disorders: Respiratory failure, pulmonary embolism, pulmonary oedema, bronchospasm, dyspnoea, cough, Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Related Acute Lung Injury (TRALI), cyanosis, hypoxemia
Gastrointestinal disorders: Nausea, vomiting, diarrhoea, abdominal pain, hepatic dysfunction
Skin and subcutaneous tissue disorders: Eczema, urticaria, rash, rash erythematous, dermatitis, pruritus, alopecia Steven-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
Musculoskeletal and connective tissue disorders: Back pain, arthralgia, myalgia, pain in extremity
Renal and urinary disorders: Acute renal failure
General disorders and administration site conditions: Fatigue, injection site reaction, pyrexia, chills, chest pain, hot flush, flushing, hyperhidrosis, malaise
Investigations: Hepatic enzymes increased, blood glucose false positive

OVERDOSE
Overdose is very unlikely to occur because Human normal immunoglobulin solution is usually administered under medical supervision. Overdose of Human normal immunoglobulin solution can lead to fluid overload and increased thickness of the blood (hyperviscosity), particularly in at-risk patients, including elderly patients or patients with impaired renal function. In case of overdose, further infusion should be halted and medical supervision is suggested along with symptomatic management.

PHARMACOLOGICAL PROPERTIES
MECHANISM OF ACTION
Human normal immunoglobulin solution having very high titres of antibodies against the infectious agents. It will provide passive immunity for the prevention and treatment of the infections. The mechanism of action has not been fully elucidated.

PHARMACODYNAMIC PROPERTIES
IVIG, human intravenous immunoglobulin, provides a broad spectrum of opsonic and neutralizing IgG antibodies against a wide variety of bacterial and viral agents reflecting the IgG activity found in the donor population. It has an IgG subclass distribution similar to that of native human plasma. IgG antibodies contained in IVIG provide passive immunity by increasing an individual's antibody titer and antigen-antibody reaction potential and prevent or modify certain infectious diseases in susceptible individuals. Adequate doses of IVIG can restore abnormally low IgG level to the normal range. The role of these antibodies and mechanism of action of IgG in different diseases has not been fully elucidated.

PHARMACOKINETIC PROPERTIES
Peak levels of IgG are reached immediately after infusion of IVIG in patients with primary immunodeficiency syndrome. Following infusion, IVIG products show a biphasic decay curve. The initial (α) phase is characterized by an immediate post-infusion peak in serum IgG and is followed by rapid decay due to equilibration between the plasma and extravascular fluid compartments until approximately half is partitioned in the extravascular space. After approximately 3-5 days, equilibrium is reached between the intra and extravascular compartments. The second (β) phase is characterized by a slower and constant rate of decay. As a class, IgG survives longer in vivo than other serum proteins. Peak levels of IgG are reached within 30 minutes after an intravenous infusion of IVIG.
Half-life of IgG in individuals with normal serum IgG concentrations is around 18–25 days while it is 12-45 days in patients with immunodeficiencies. The half-life of IgG can vary considerably from person to person, however. In particular, high serum concentrations of IgG and hypermetabolism associated with fever and infection have been seen to coincide with a shortened half-life of IgG. IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

NONCLINICAL PROPERTIES
ANIMAL TOXICOLOGY OR PHARMACOLOGY
Being human plasma-derived proteins, safety testing in animals is not particularly relevant to correlate the safety of use in man. Moreover, as these human plasma proteins are more immunogenic to animals than humans, reliability and productivity of pre-clinical testing further diminish.
In animals, single-dose toxicity testing is of little relevance and does not permit the evaluation of toxic and lethal doses or a dose-effect relationship. Repeated dose toxicity testing is impractical due to the development of antibodies to heterogeneous protein in animal models.

DESCRIPTION
Human Normal Immunoglobulin for Intravenous use (IVIG) is a sterile and solvent-detergent (S/D) treated preparation of highly purified Immunoglobulin G (IgG) intended for intravenous use. It is prepared from the large pools of the human plasma obtained from the healthy donors. IVIG is used to provide passive immunity by increasing an individual's antibody titer and antigen-antibody reaction potential. IVIG also helps to prevent or modify certain infectious diseases in susceptible individuals.

PRODUCT SAFETY
Collected blood plasma which used in manufacturing of IVIG, screened for the mandatory infectious diseases. Only on being declared negative to HBsAg, HIV I & II antibodies, HCV RNA and antibodies against HCV the plasma is used for processing.
The manufacturing procedure incorporates two dedicated orthogonal virus clearance steps ensuring viral safety of the product. This includes solvent detergent treatment and virus retentive filtration. The use of 20 nm virus retentive filter provides additional safety against enveloped and non-enveloped virus. The manufacturing process of Globucel® XP shows significant viral reduction and inactivation, demonstrated by virus validation study.

After manufacturing, the product is tested as per specification and that also indicates the product is non-reactive to viruses like HIV, HBsAg, HCV. Multiple steps have been applied to product safety assurance; there is a very remote probability that unknown infectious agents may be present in these products like newer emerging viruses and theoretical CJD (Creutzfeldt Jakob Disease). The process parameters, characterizations and final product quality are designed such, that they meet the regulatory requirements.
Abbreviation: IVIG: Intravenous immunoglobulins; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; HBsAg: Hepatitis B surface antigen.

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

SHELF-LIFE
Refer Outer Carton and Vial Label for Expiry. Do not use after Expiry date.

PACKAGING INFORMATION
Container & Closure : USP Type-I clear glass vial with Bromobutyl rubber stopper
IVIG is supplied as 5% solution containing 5 g of Human Normal Immunoglobulin per 100 ml for intravenous administration.

STORAGE AND HANDLING INSTRUCTIONS
Store at +2°C to +8°C.
Partially used vials should be discarded.
Do not freeze.
Before use, visually inspect the medicine. The solution must be clear or slightly opalescent and colorless or pale yellow. Do not use if the solution is cloudy or has deposits.
Keep out of reach and sight of children.
Store in the original container to protect from light.

Report suspected adverse reaction at: **Hemofluidsafety@intaspharma.com**
DATE OF PREPARATION: 31/08/24

Manufactured and Marketed by:
INTAS PHARMACEUTICALS LTD.
Plot No. 496/1/A&B, Sarkhej-Bavla Highway,
Village: Matoda, Taluka: Sanand,
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AW-229-00

Front Side **Back Side**

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Department	QA	Production	Regulatory	Marketing	Medical	QA	QA
Sign							
Date							
Name							
Designation							

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Size : 130 x 270 mm
Type of Paper : Maplitho
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Colour Shade No. : Black
No. of fold : 4
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