HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YIMMUGO safely and effectively. See full prescribing information for YIMMUGO.

YIMMUGO (immune globulin intravenous, human - dira), 10% liquid
Initial U.S. Approval: 2024

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin intravenous (IGIV) products, including YIMMUGO. (5.3)**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of IGIV products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. YIMMUGO does not contain sucrose. (5.4)**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer YIMMUGO at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. (2.1, 2.3, 5.3)**

----------INDICATIONS AND USAGE----------

YIMMUGO is an immune globulin intravenous, human - dira, 10% liquid indicated for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age or older. (1)

----------DOSAGE AND ADMINISTRATION----------

Intravenous use only.

Dose	Infusion Number	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
300–800 mg/kg (3–8 mL/kg) every 3–4 weeks	For the 1st infusion	0.5 mg/kg/min (0.005 mL/kg/min) for 30 minutes	Gradually increase every 30 minutes up to 3.0 mg/kg/min (0.03 mL/kg/min).
300–800 mg/kg (3–8 mL/kg) every 3–4 weeks	From the 2nd infusion	0.5 mg/kg/min (0.005 mL/kg/min) for 30 minutes	Gradually increase up to 13 mg/kg/min (0.13 mL/kg/min).

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; consider discontinuing YIMMUGO if renal function deteriorates. (2.3, 5.4)
- For patients at risk of renal dysfunction or thrombotic events, administer YIMMUGO at the minimum dose and infusion rate practicable. (2.3, 5.4, 5.3)

----------DOSAGE FORMS AND STRENGTHS----------

YIMMUGO is a solution containing 10% IgG (100 mg/mL): 5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL. (3)

----------CONTRAINDICATIONS----------

- History of anaphylactic or severe systemic reaction to human immune globulin. (4)
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. (4)

----------WARNINGS AND PRECAUTIONS----------

- IgA-deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions to YIMMUGO. Epinephrine should be available for immediate treatment of severe acute hypersensitivity reactions. (5.1)
- Hemolysis, either intravascular or due to enhanced red blood cell sequestration can develop subsequent to YIMMUGO treatments. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia. (5.2)
- In patients at risk of developing acute renal failure, monitor renal function, including blood urea nitrogen (BUN) and serum creatinine, and urine output. (5.4)
- Hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia can occur in patients receiving IGIV treatment (5.5).
- Aseptic meningitis syndrome (AMS) has been reported with IGIV treatments, especially with high doses or rapid infusion. (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.7)
- YIMMUGO is made from human blood and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease [vCJD] agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions in ≥5% of clinical trial patients were headache, upper respiratory tract infections, fatigue, nausea and increased blood pressure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Passive transfer of antibodies may:

- Transiently interfere with the immune response to live virus vaccines, e.g. measles, mumps, rubella and varicella. (7.2)
- Interact with loop diuretics. (7.4)
- Confound the results of serological testing. (7.3, 5.10)

----------USE IN SPECIFIC POPULATIONS----------

Geriatric: In patients over age 65 who are at risk of developing thrombosis or renal insufficiency, infuse YIMMUGO at the minimum rate practicable and do not exceed the recommended dose. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2024

FULL PRESCRIBING INFORMATION:

CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin intravenous (IGIV) products, including YIMMUGO** *[see Warnings and Precautions (5.3), Patient Counseling Information (17)]***.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of IGIV products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. YIMMUGO does not contain sucrose** *[see Warnings and Precautions (5.4)]***.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer YIMMUGO at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity** *[see Dosage and Administration (2.1, 2.3), Warnings and Precautions (5.3)]***.**

1 INDICATIONS AND USAGE

YIMMUGO (immune globulin intravenous, human – dira), is a 10% immune globulin liquid, indicated for the treatment of primary humoral immunodeficiency (PI) including but not limited to the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID) in patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dosage

Table 1: Recommended Dosage and Administration

Dose	Infusion Number	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
300–800 mg/kg (3–8 mL/kg) every 3–4 weeks	For the 1st infusion	0.5 mg/kg/min (0.005 mL/kg/min) for 30 minutes	Gradually increase every 30 minutes up to 3.0 mg/kg/min (0.03 mL/kg/min).
300–800 mg/kg (3–8 mL/kg) every 3–4 weeks	From the 2nd infusion	0.5 mg/kg/min (0.005 mL/kg/min) for 30 minutes	Gradually increase up to 13 mg/kg/min (0.13 mL/kg/min).

The dosage may be adjusted over time to achieve the desired trough levels and clinical response.

2.2 Preparation and Handling

- YIMMUGO is a clear to slightly opalescent, colorless to pale yellow solution. Inspect visually for particulate matter and discoloration prior to administration, whenever the solution and container permit. Do not use if the liquid is cloudy or turbid, discolored, or if it contains visible particulate matter.
- Do not shake.
- YIMMUGO should be at room or body temperature at the time of administration.
- Do not mix with other IGIV products or other intravenous medications.

- Do not dilute.
- YIMMUGO is for single use only. It contains no preservatives. Promptly use any vial that has been entered. Discard partially used vials and unused product in accordance with local requirements.
- Do not use YIMMUGO after expiration date on the product label. *[see How Supplied/Storage and Handling (16)]*

2.3 Administration

Administer YIMMUGO at room temperature or body temperature by the intravenous route. Do not mix with any intravenously administered medications. For rate of infusion, refer to Table 1. Monitor patient vital signs throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients judged to be at risk for renal dysfunction or thrombotic events, administer YIMMUGO at the minimum infusion rate practicable, and consider discontinuation of administration if renal function deteriorates *[see Boxed Warning, Warnings and Precautions (5.4, 5.3)].*

Hydrate the patient adequately prior to the initiation of infusion.

3 DOSAGE FORMS AND STRENGTHS

YIMMUGO is a solution containing 10% IgG (100 mg/mL): 5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL.

4 CONTRAINDICATIONS

- YIMMUGO is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- YIMMUGO is contraindicated in patients with IgA-deficiency who have antibodies against IgA and a history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions, including anaphylaxis, have been reported after YIMMUGO administration. *[see Contraindications (4)]*. In case of hypersensitivity, discontinue YIMMUGO infusion immediately and institute appropriate treatment. Epinephrine should be available for immediate treatment of severe acute hypersensitivity reactions.

YIMMUGO contains less than or equal to 300 micrograms per milliliter of IgA *[see Description (11)]*. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. YIMMUGO is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity reaction *[see Contraindications (4)].*

5.2 Hemolysis

Hemolysis has been reported after YIMMUGO administration. IGIV products, including YIMMUGO, may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis.[1] Delayed hemolytic anemia can develop subsequent to IGIV treatment due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis.The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g. ≥2 g/kg given either as a single administration or divided over several days), and non-O blood group. Other individual patient factors, such as underlying inflammatory state (as may be reflected by elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV, but their role is uncertain.

Monitor patients for clinical signs and symptoms of hemolysis *[see Patient Counseling Information (17)]*. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit are observed after YIMMUGO infusion, perform confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with anemia after receiving IGIV, perform cross-matching to avoid exacerbating ongoing hemolysis.

5.3 Thrombosis

Thrombosis may occur following treatment with immune globulin products,[2,3] including YIMMUGO. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including patients with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer YIMMUGO at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity *[see Boxed Warning, Dosage and Administration (2), Patient Counseling Information (17)]*.

5.4 Renal Failure

Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering YIMMUGO. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic drugs, or age of >65 years), administer YIMMUGO at the minimum infusion rate practicable *[see Boxed Warning and Dosage and Administration (2.3)].*

Conduct periodic monitoring of renal function and urine output in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of YIMMUGO and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing YIMMUGO *[see Patient Counseling Information (17)].*

5.5 Hyperproteinemia, increased serum viscosity and hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV treatment, including YIMMUGO. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.

5.6 Aseptic Meningitis Syndrome

Aseptic meningitis syndrome (AMS) may occur infrequently in patients following IGIV treatments, including YIMMUGO. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[4] AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting *[see Patient Counseling Information (17)]*. Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the

granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting signs and symptoms of AMS, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.7 Transfusion-Related Acute Lung Injury

Noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] may occur in patients following IGIV treatment,[4] including YIMMUGO. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected immediately stop IGIV and perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in both the product and the patient's serum *[see Patient Counseling Information (17)]*.

TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Transmissible Infectious Agents

Because YIMMUGO is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. The risk of infectious agent transmission has been reduced by screening plasma donors and by including virus inactivation as well as virus and prion removal steps in the manufacturing process of YIMMUGO.

All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols at 1-800-520-2807. Discuss the risks and benefits of YIMMUGO use with patient before prescribing or administering this product.*[see Patient Counseling Information (17)]*.

5.9 Monitoring Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of YIMMUGO and at appropriate intervals thereafter *[see Warnings and Precautions (5.4)]*.
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis *[see Warnings and Precautions (5.3)]*.
- If signs and/or symptoms of hemolysis are present after an infusion of YIMMUGO, perform appropriate laboratory testing for confirmation *[see Warnings and Precautions (5.2)]*.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and the patient's serum *[see Warnings and Precautions (5.7)]*.

5.10 Interference with Laboratory Tests

After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Primary humoral immunodeficiency (PI)

In an open-label, prospective, multicenter, multinational trial, the efficacy, safety, and pharmacokinetic properties of YIMMUGO as replacement therapy in patients with PI were investigated in 67 patients (including 12 children and 6 adolescents).[5,6] Patients received a dose between 200 mg to 800 mg per kg body weight (bw) every 3 or 4 weeks, for a treatment period of approximately 12 months. The initial dose and dosage interval was consistent with the patient's prestudy IGIV treatment *[see Clinical Studies (14)]*.

There were two serious adverse events (SAEs) related to YIMMUGO, occurring in two patients: anaphylactic reaction, and severe neutropenia. Both SAEs led to discontinuation of YIMMUGO. One patient also had mild hemolysis and positive Coomb's test.

Adverse reactions (AR) occurring in ≥5% of patients are presented in Table 2.

Table 2: Adverse Reactions * in ≥ 5% of Patients

Adverse Reaction MedDRA - Preferred Term	Number (%) of Patients with AR N = 67	Number (%) of Infusions N_{inf} = 923
≥1 Adverse reaction	**39 (58)**	**93 (10)**
Headache	13 (19)	22 (2)
Upper respiratory tract infections	8 (12)	8 (<1)
Fatigue	5 (8)	8 (<1)
Nausea	4 (6)	5 (<1)
Increased blood pressure	4 (6)	4 (<1)

* Adverse reactions were identified as all AEs that were temporally associated with an infusion (occurred during infusion or within 72 h after the end of an infusion) or that were assessed as related.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified and reported during the post-approval use of IGIV products:

- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, respiratory failure, hypoxemia, pulmonary edema, dyspnea, wheezing, cough, bronchospasm, pulmonary embolism.
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension, phlebitis, pallor, angina, tachycardia, bradycardia, palpitations, myocardial infarction, cyanosis.
- *Neurological:* Coma, loss of consciousness, seizures, (acute) encephalopathy, tremor, aseptic meningitis syndrome, migraine, speech disorder, paresthesia, hypoesthesia, photophobia.
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis, eczema, erythematous rash, dermatitis, pruritus, alopecia, urticaria.
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain, diarrhea.

- *Renal:* Acute renal failure, osmotic nephropathy, renal pain.
- *Hematologic:* Pancytopenia, leukopenia, hemolysis.
- *Musculoskeletal:* Musculoskeletal pain, muscle spasm, arthralgia, myalgia, muscle stiffness.
- *General disorders and administration site conditions:* Pyrexia, rigors, injection-site reactions, chills, flushing, lethargy, malaise, burning sensation.
- *Psychiatric disorders:* Confusion, anxiety, agitation, nervousness.
- *Metabolic and nutritional:* Fluid overload, (pseudo) hyponatremia.
- *Immune system disorders:* Hypersensitivity (e.g. anaphylaxis, allergic reaction), angioedema.
- *Investigations*: Falsely elevated erythrocyte sedimentation rate, positive direct antiglobulin (Coombs') test, increased hepatic enzymes.

7 DRUG INTERACTIONS

7.1 Intravenous Products

Clinical studies have not evaluated mixture of YIMMUGO (immune globulin intravenous, human-dira) with other intravenous drugs and solutions. Administer YIMMUGO separately from other drugs or medications which the patient may be receiving. Do not mix YIMMUGO with other IGIVs products.

7.2 Live Virus Vaccines

Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response.[7] Inform the immunizing physician of recent therapy with YIMMUGO so that appropriate measures may be taken *[see Patient Counseling Information (17)]*.

7.3 Serological Testing

Various passively transferred antibodies in immunoglobulin preparation may lead to misinterpretation of the results of serological testing.

7.4 Loop Diuretics

Avoid concomitant use of loop diuretics. Concomitant use of loop diuretics with IGIV may additionally contribute to an increased blood viscosity and subsequently increase the risk of thromboembolic events.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with YIMMUGO. It is not known whether YIMMUGO can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively. YIMMUGO should be given to pregnant women only if clearly needed.

8.2 Lactation

Risk Summary

No human data are available to indicate the presence or absence of drug-associated risk. Immune globulins are excreted into human milk. The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for YIMMUGO and any potential adverse effects on the breast-fed infant from YIMMUGO or from the underlying maternal condition.

8.4 Pediatric Use
YIMMUGO was evaluated in 18 pediatric patients (12 children age 2 to less than 12 years and 6 adolescents age 12 – 16 years) with PI. Dose requirements did not differ between children and adults. Safety and effectiveness has not been studied in pediatric patients with PI who are under the age of 2 years *[see Clinical Studies(14)]*.

8.5 Geriatric Use
Clinical studies of YIMMUGO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients . Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Boxed Warning, Warnings and Precautions (5.4, 5.3)]*. Do not exceed recommended doses, and administer YIMMUGO at the minimum infusion rate practicable.

10 OVERDOSAGE
Overdose may lead to fluid overload and hyperviscosity. Patients at risk of complications of fluid overload and hyperviscosity include infants, elderly patients and those with cardiac or renal impairment.

11 DESCRIPTION
YIMMUGO, immune globulin intravenous, human – dira, is a highly purified, sterile, non-pyrogenic, ready-to-use 10% liquid preparation of concentrated polyclonal human immune globulin G (IgG) antibodies for intravenous administration. The product is a clear to slightly opalescent liquid, which is colorless to pale yellow. The active ingredient is human IgG purified from human Source Plasma and processed using a combination of cold ethanol fractionation, caprylic acid precipitation, as well as anion and cation exchange chromatography. YIMMUGO contains 100 ± 10 mg/mL protein, of which not less than 96% is IgG. The distribution of IgG subclasses is similar to that of normal plasma. YIMMUGO is formulated in water for injection containing 0.27 to 0.33 mmol/mL glycine, 2 to 20 mcg/mL polysorbate 80, with pH 4.4 to 5.2 and osmolality ranges of 280 to 380 mOsmol/kg. YIMMUGO contains not more than 300 mcg/mL of IgA. YIMMUGO does not contain carbohydrate stabilizers (e.g., sucrose, maltose) or preservatives.
YIMMUGO is prepared from pooled plasma obtained from healthy volunteer donors. Each plasma donation used for the manufacture of YIMMUGO is collected from FDA-licensed facilities. Plasma donations must test negative for hepatitis B virus (HBV) surface antigen (HBsAg), antibodies to human immunodeficiency virus (HIV) strains 1 and 2 (anti-HIV-1/2), and antibodies to the hepatitis C virus (anti-HCV) as determined by enzyme immunoassay (EIA). In addition, samples from manufacturing pools must test non-reactive for HIV RNA, HCV RNA, HBV DNA and Hepatitis A Virus (HAV) RNA, by Nucleic Acid Amplification Testing (NAT). Parvovirus B19 (B19V) DNA is also tested by NAT and must not exceed 10^4 IU/mL in the manufacturing pool.
The manufacturing process of YIMMUGO employs several steps to remove/inactivate adventitious viruses to further increase the margins of safety. These steps include caprylic acid, low pH treatment, anion exchange chromatography (AEX) and nanofiltration. Virus clearance studies with a scaled-down process have been performed for these steps to determine their capacity to inactivate or remove both enveloped and non-enveloped viruses. The results are shown in Table 3.

Table 3: Virus Clearance Data (Log_{10}) for YIMMUGO for enveloped (HIV, BVDV, PRV) and non-enveloped viruses (HAV, EMCV, B19V, PPV, HEV)

Test Virus → ↓ Step	HIV	BVDV	PRV	HAV	EMCV	B19V*	PPV	HEV*
Caprylic Acid Treatment	**≥ 5.64**	**≥ 5.97**	**≥ 6.21**	**≥ 4.39**	n.d.	**2.48**	**1.01**	**≥ 4.96**
Low pH Treatment	**≥ 6.63**	< 1	n.d.	n.d.	n.d.	n.d.	< 1	n.d.
Anion Exchange Chromatography	n.d.	**2.62**	n.d.	**≥ 3.95**	n.d.	**≥ 5.86**	**3.21**	n.d.
Virus Filtration	**≥ 4.72**	**≥ 4.72**	n.d.	**≥ 4.37**	**≥ 4.93**	**≥ 4.33**	**6.12**	n.d.
Total Virus Clearance †	**≥ 16.99**	**≥ 13.31**	**≥ 6.21**	**≥ 12.71**	**≥ 4.93**	**≥ 12.67**	**10.34**	**≥ 4.96**

n.d. not determined.

* Polymerase chain reaction (PCR) was used to quantify B19V and HEV genome counts (all other viruses were quantified by in-vitro infectivity assays, using mammalian cell lines).

† Log_{10} reduction factors of 1 or smaller were not considered for calculation of total virus clearance.

BVDV, bovine viral diarrhea virus, a model for hepatitis C virus; **PRV**, pseudorabies virus, a model for hepatitis B virus; **EMCV**, encephalomyocarditis virus, a model for hepatitis A virus; **B19V**, parvovirus B19; **PPV**, porcine parvovirus, a model for B19V; **HEV**, hepatitis E virus.

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a model for CJD and its variant vCJD. Several of the production steps have been shown to decrease TSE infectivity of the experimental model agent. TSE reduction steps include caprylic acid treatment followed by depth filtration (in sequence, a total of ≥ 5.99 log_{10}). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

YIMMUGO provides a broad spectrum of opsonizing and neutralizing immune globulin G (IgG) antibodies against a wide variety of pathogens and their toxins, which helps to avoid recurrent serious opportunistic infections. The mechanism of action has not been fully elucidated but may include immunomodulatory effects.

12.2 Pharmacodynamics

YIMMUGO contains mainly IgG with a broad spectrum of antibodies against various infectious agents, reflecting the IgG activity found in the donor population. YIMMUGO which is prepared from pooled plasma from not less than 1,000 donors, has an IgG subclass distribution similar to that of native human plasma. Adequate doses of IGIV can restore an abnormally low IgG level to the normal range. Standard pharmacodynamics studies were not performed.

12.3 Pharmacokinetics

The pharmacokinetic parameters for YIMMUGO were determined in an open-label, prospective, multicenter, multinational clinical trial in 57 patients with PI *[see Clinical Studies (14)]*. IgG levels for determination of PK parameters were measured after the 7th (3-week schedule, n = 10) or 5th infusion (4-week schedule, n = 47) in 57 patients (6 to <76 years of age). Patients for whom PK data was available received doses of YIMMUGO between 280 mg/kg to 800 mg/kg. The mean half-life of YIMMUGO for adults was 24.8–29.9 days depending

on the treatment schedule (see Table 4). PK parameters did not indicate any clinically relevant differences between the 3-week and 4-week schedule.

Table 4: Pharmacokinetic Parameters of YIMMUGO at Steady State

a) PK Parameters: 3 Week Schedule - Mean (SD)

Parameter	6-<12 Years	12-<17 Years	17-<76 Years
N*	**2**	**1**	**7**
C_{max} (mg/mL)	19.6 (3.9)	34.8	32.3 (6.3)
C_{trough} (mg/mL)	8.2 (0.2)	13	10.4 (2.4)
AUC_{tau} (day × g/L)	238.7 (5.9)	477	398.4 (99)
CL_{ss} (mL/day/kg)	2 (0.3)	1.2	1.4 (0.3)
V_{ss} (mL/kg)	69.4 (23)	27	53.5 (15.7)
Half-life (days)	29.5, n=1	15.5	24.8 (5.1), n=5

b) PK Parameters: 4 Week Schedule - Mean (SD)

Parameter	6-<12 Years	12-<17 Years	17-<76 Years
N*	**3**	**5**	**39**
C_{max} (mg/mL)	24.7 (1.2), n=2	22.2 (2.3), n=4	27.1 (6.3)
C_{trough} (mg/mL)	7.1 (1.2), n=3	9.1 (1.7), n=5	8.1 (2.5)
AUC_{tau} (day × g/L)	392.1 (19.7), n=2	415.1 (94.9), n=4	397 (103.6), n=36
CL_{ss} (mL/day/kg)	1 (0.1), n=2	0.9 (0.3), n=4	1.3 (0.5), n=36
V_{ss} (mL/kg)	74.6 (7.2), n=2	56.5 (12.8), n=4	61.8 (39.1), n=35
Half-life (days)	57.5, n=1	31.7 (3), n=2	29.9 (12.4), n=22

* Divergent number of subjects for individual PK parameters are indicated behind values.

Abbreviations: AUC_{tau} = area under the concentration-time curve calculated from start to end of the dosing interval; CL_{ss} = clearance at steady state; C_{max} = maximum serum concentration; C_{trough} = trough concentration at steady state; n = number of subjects with data; SD = standard deviation; V_{ss} = volume of distribution at steady state

Although no systematic study was conducted to evaluate the effect of sex on the pharmacokinetics of YIMMUGO, subgroup analysis between males (n= 37) and females (n = 30) revealed no clinically relevant differences in exposure and IgG trough levels.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effects of YIMMUGO or its effects on fertility.

13.2 Animal Toxicology and/or Pharmacology

A single dose toxicology study in male and female Sprague Dawley rats was conducted. Study endpoints included clinical and hematological evaluations, post-mortem analyses, and sensory-motor activity evaluations on days 1 and 15 post-dosing. Under the conditions of this study, the single intravenous infusion administration of YIMMUGO at a dose level of 2 g/kg body weight given at a rate of 20 mL/kg for 40 minutes was not associated with any adverse findings.

14 CLINICAL STUDIES

Trial 991(NCT02810444): The safety, effectiveness and pharmacokinetics of YIMMUGO as replacement therapy in patients with PI were investigated in an open-label, prospective, multicenter, multinational trial. The study planned to enroll patients 2 to 75 years of age with PI who had established IGIV therapy for at least 3 months with a constant dose, and at least one IgG trough level of ≥5g/L during the previous 3 months. The patients were to receive YIMMUGO at doses between 0.2 to 0.8 g per kg body weight (bw) at either 3-week (Q3W) or 4-week (Q4W) intervals for a period of 12 months. The initial dose and dosage interval had to be consistent with the subject's prestudy IGIV treatment and doses were to be adjusted for changes in weight or as medically indicated.

The primary efficacy outcome measure was the rate of serious bacterial infections (SBI), defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscesses, or bacterial meningitis over a period of 12 months. The predefined success criteria was demonstration of rate of less than one acute SBI per patient per year. Additional efficacy outcome measures included occurrence of any infection, time to resolution of infections, use of antibiotics, the number of days missed from work/school, and hospitalizations.

The trial enrolled 67 patients with a mean age of 35 years (range 2 to 74 years). There were 18 pediatric patients (including 12 children and 6 adolescents), and 5 patients ≥65 years of age. The study population was mainly white (n=66; 98.5%) and males represented 55% (n=37). The most common underlying cause of PI was CVID (n=53; 79%). Other etiologies included XLA (n=10; 15%), congenital agammaglobulinaemia (n=2; 3%), congenital hypogammaglobulinaemia (n=1; 1.5%), and specific antibody defect (n=1; 1.5%).

Patients received a dose ranging from 200 mg to 833 mg per kg body weight (bw) every 3 (n=12) or 4 weeks (n=55), for a treatment period of approximately 12 months. Infusions were initiated at a rate of 0.5 mg/kg/min (0.005 mL/kg/min) for the first 30 minutes, and, if tolerated, could be increased to a maximum tolerated rate not exceeding 13 mg/kg/min (0.13mL/kg/min). During the study 10 patients required a dose adjustment (increase) due to low IgG levels (including 7 patients who had trough levels <5 g/L). Additionally, 2 patients required

dose adjustment (increase) due to infections, and 1 patient required a dose reduction due to an adverse reaction (worsening of fatigue).

The study demonstrated that treatment with YIMMUGO resulted in less than one SBI per person-year. A total of five acute SBIs occurred among study participants. All five acute SBIs were bacterial pneumonia. A summary of efficacy outcomes is shown in Table 5.

Table 5: Summary of Efficacy Results in Trial 991

Category	Results
Number of Patients	67 patients with 67.6 years on study
Infections	
Annualized rate of acute SBIs	0.07 acute SBIs/person-year (99% CI 0.21)
Annualized rate of other infections	2.7 infections/person-year
Time to resolution of infection*	7 (1, 172) days†
Antibiotics	
Number of patients with therapeutic antibiotic use	35 subjects (52.2%)
Number of days on therapeutic antibiotics*	9.5 (3, 35) days
Time lost from work/school	
Number of patients who lost ≥1 day due to infection	26 subjects (38.8%)
Number of days lost from work/school due to infection*	6 (1, 85) days
Hospitalizations due to infection	
Number of patients with hospitalizations due to infection	3 subjects (4.5%)
Number of days hospitalized*	2 (2, 20) days
Annualized rate of hospitalization due to infection	0.36 days/person-year

*Number of days presented in median (min, max) among patients with events of a duration of ≥1 day; maximum duration was used if there were multiple events.
†Two patients had unresolved infections at the last follow-up visit.

15 REFERENCES

1. Bellac, CL, Hottiger T, Jutzi MP, Bögli-Stuber K, Sänger M, Hanschmann K-M, et al. The role of isoagglutinins in intravenous immunoglobulin-related hemolysis. Transfusion 2015;55 Suppl 2:S13-22.
2. Dalakas, MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology 1994;44:223-6.
3. Wolberg AS, Kon RH, Monroe DM, Hoffman M. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. Am J Hematol 2000;65:30-4.
4. Guo, Y, Tian X, Wang X,Xiao Z.Adverse effects of immunoglobulin therapy. Front Immunol 2018;9:1299.
5. Kriván G, Borte M, Harris JB, Lumry WR, Aigner S, Lentze S, et al. Efficacy, safety and pharmacokinetics of a new 10% normal human immunoglobulin for intravenous infusion, BT595, in children and adults with primary immunodeficiency disease. Vox Sang 2022;117:1153-62.
6. Kriván G, Borte M, Soler-Palacin P, Church JA, Csurke I, Harris JB, et al. BT595, a 10% human normal immunoglobulin, for replacement therapy of primary immunodeficiency disease: results of a subcohort analysis in children. J Clin Immunol 2023;43:557-67.

7. Siber GA, Werner BG, Halsey NA, Reid R, Almeido-Hll J, Garrett SC, et al. Interference of immune globulin with measles and rubella immunization. J Pediatr 1993;122:204-11.

16 HOW SUPPLIED/STORAGE AND HANDLING

YIMMUGO is supplied in 5, 10 and 20 gram single-dose vials.

Package NDC	Container NDC	Size	Gram Protein
83372-605-01	83372-605-02	50 mL	5
83372-605-11	83372-605-12	100 mL	10
83372-605-21	83372-605-22	200 mL	20

- The components used in the packaging for YIMMUGO are not made with natural rubber latex.
- Keep YIMMUGO in its original carton to protect it from light.
- Refrigerate between 2°C to 8°C (36°F to 46°F).
- Do not use after expiration date.
- Within the expiration date, the product may be stored at room temperature (more than 8°C and up to 25°C/ more than 46°F and up to 77°F) for a single period not exceeding 6 months. Once the product has been taken out of the refrigerator, it must not be returned to the refrigerator. Please record the date of the beginning of storage at room temperature on the product carton.
- Do not freeze. Do not use any solutions that have been frozen.

17 PATIENT COUNSELING INFORMATION

Inform patients of the early signs of hypersensitivity reactions to YIMMUGO (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis), and advise them to notify their physician if they experience any of these symptoms *[see Warnings and Precautions (5.1)]*.

Instruct patients taking YIMMUGO to immediately report symptoms of:

- Acute Renal Dysfunction and Acute Renal Failure which may include decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath. Such symptoms may suggest kidney damage *[see Boxed Warning, Warnings and Precautions (5.4)]*.
- Thrombosis which may include pain and/or swelling of an arm or legs/feet with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, acute chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body *[see Warning and Precaution (5.3)]*.
- Aseptic Meningitis Syndrome (AMS) which may include severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting *[see Warnings and Precautions (5.6)]*.
- Hemolysis which may include fatigue, increased heart rate, yellowing of skin or eyes, dark- colored urine *[see Warnings and Precautions (5.2)]*.
- Transfusion-Related Acute Lung Injury (TRALI) which includes trouble breathing, chest pain, blue lips or extremities, fever *[see Warnings and Precautions (5.7)]*.

Inform patients that YIMMUGO:

- Is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses, and theoretically, the CJD agent). While the risk that YIMMUGO can transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing, patients should report any symptoms that concern them *[see Description (11) and Warnings and Precautions (5.8)]*.

- Can interfere with their immune response to live virus vaccines (e.g., measles, mumps, rubella, and varicella). Instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations *[see Drug Interactions (7.2)]*.

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