HIGHLIGHTS OF PRESCRIBING INFORMATION

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

QIVIGY (immune globulin intravenous, human-kthm) 10% solution
Initial U.S. Approval: 2025

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- Thrombosis may occur with immune globulin products, including QIVIGY. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. *(5.2)*
- Renal dysfunction, acute renal failure, osmotic nephrosis may occur in predisposed patients with immune globulin intravenous (IGIV) products, including QIVIGY. Such events require immediate medical intervention; if not recognized or managed appropriately, may result in persistent or significant disability or incapacity or lead to fatal outcome. *(5.3)*
- For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer QIVIGY 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. *(5.2, 5.3)*

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

QIVIGY (immune globulin intravenous, human-kthm) 10% solution is indicated for treatment of adults with primary humoral immunodeficiency (PI). (1)

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

Intravenous Administration Only.

Dose	Infusion number	Initial Infusion Rate	Maintenance Infusion Rate (as tolerated)
300 - 800 mg/kg every 3-4 weeks	For the 1st infusion	1 mg/kg/min (0.01 mL/kg/min) for 30 minutes	Increase every 30 minutes to a maximum of 8 mg/kg/min (0.08 mL/kg/min)
300 - 800 mg/kg every 3-4 weeks	From the 2nd infusion	2 mg/kg/min (0.02 mL/kg/min) for 15 minutes	Increase every 15 minutes to a maximum of 8 mg/kg/min (0.08 mL/kg/min)

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

QIVIGY is a sterile, liquid solution 10% containing 100 mg/mL, in the following presentation:

- 5 g Immune Globulin per 50 mL single dose vial. (3)
- 10 g Immune Globulin per 100 mL single dose vial. (3)

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

- Patients with history of anaphylactic or severe systemic reactions to human immune globulins. (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity. (4)

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

- Hypersensitivity Reactions: In case of a severe hypersensitivity reaction, discontinue QIVIGY infusion, and manage as appropriate. IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. (5.1)
- Thrombotic events: Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for patients at risk of hyperviscosity. (5.2)
- Hyperproteinemia, hyperviscosity, hyponatremia, or pseudohyponatremia may occur in patients receiving IGIV therapy. (5.4)
- Renal Injury: Ensure patients are not volume depleted before administering QIVIGY. Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients receiving QIVIGY prior to initial infusion and at appropriate intervals thereafter. (5.3)
- Aseptic Meningitis Syndrome (AMS) may occur, more frequently in association with high doses of IGIV or rapid infusion. (5.5)
- Hemolysis: Risk factors include high doses and non-O blood group. Monitor patients for hemolysis and hemolytic anemia. (5.6)
- Transfusion-related acute lung injury (TRALI): Monitor patients for symptoms of TRALI and manage using oxygen therapy with adequate ventilatory support as appropriate. (5.7)
- Transmission of infectious agents: QIVIGY is made from human plasma and may carry a risk of transmitting infectious agents. (5.8)

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

The most common adverse reactions observed in ≥ 5% of patients were headache, fatigue, nausea, infusion-related reaction, Coombs direct test positive, sinusitis, dizziness and diarrhea. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Kedrion Biopharma Inc. at 1-855-3KDRION (1-855-353-7466) or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

The passive transfer of antibodies may:

- Interfere with the response to live virus vaccines, such as measles, rubella, mumps and varicella. (7)
- Result in misleading positive results in serological testing. (5.9, 7)

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

Geriatric: In patients over 65 years of age do not exceed the recommended dose and infuse QIVIGY at the minimum infusion rate practicable. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2025

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 products, including QIVIGY. 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 *[see Warnings and Precautions (5.2)]*.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis may occur with immune globulin intravenous (IGIV) products in predisposed patients. Such events require immediate medical intervention, if not recognized or managed appropriately, may result in persistent or significant disability or incapacity or lead to fatal outcome. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs *[see Warnings and Precautions (5.3)]*.**
- **For patients at risk of thrombosis, renal dysfunction or failure, administer QIVIGY at the minimum dose available and the minimum 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 Warnings and Precautions (5.2, 5.3)]*.**

1 INDICATIONS AND USAGE

QIVIGY (immune globulin intravenous, human-kthm) 10% solution is indicated for the treatment of adults with Primary Humoral Immunodeficiency (PI).

This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Table 1. Recommended Dosage for QIVIGY

Dose	Infusion number	Initial Infusion Rate	Maintenance Infusion Rate (as tolerated)
300 - 800 mg/kg every 3-4 weeks	For the 1st infusion	1 mg/kg/min (0.01 mL/kg/min) for 30 minutes	Increase every 30 minutes to a maximum of 8 mg/kg/min (0.08 mL/kg/min)
300 - 800 mg/kg every 3-4 weeks	From the 2nd infusion	2 mg/kg/min (0.02 mL/kg/min) for 15 minutes	Increase every 15 minutes to a maximum of 8 mg/kg/min (0.08 mL/kg/min)

- Adjust frequency and dosage overtime to achieve target serum IgG levels and clinical response.
- If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.
- In patients judged to have a potential increased risk for developing acute renal failure or thrombosis, QIVIGY should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IGIV discontinuation should be considered [see Administration and Warnings and Precautions (2.3, 5.3)].

Measles pre-/post exposure prophylaxis

Post-exposure prophylaxis

If a patient has been exposed to measles, a dose of 400 mg/kg (4 mL/kg) of QIVIGY should be administered as soon as possible after exposure.

Pre-exposure prophylaxis

If a patient routinely receives a dose of less than 400 mg/kg of QIVIGY every 3 to 4 weeks (less than 4 mL/kg) and is at risk of measles exposure (i.e. traveling to a measles endemic area), administer a dose of at least 400 mg/kg (4 mL/kg) just prior to the expected measles exposure.

2.2 Preparation and Handling

- QIVIGY is a clear or slightly opalescent and colorless or pale-yellow solution. Inspect QIVIGY visually for particulate matter and discoloration prior to administration, whenever the solution and container permit. Do not use if the solution is cloudy, turbid, or if it contains particulate matter or deposits.
- Do not shake.
- Do not dilute.
- QIVIGY should be brought to room temperature before use (up to 25 °C [77 °F]).
- Keep the vial in the outer carton.
- If the packaging shows any signs of tampering, do not use the product and notify Kedrion Biopharma Inc. immediately at 1-855-3KDRION (1-855-353-7466).
- The QIVIGY vial is for single use only. Any vial that has been opened must be used immediately. QIVIGY contains no preservative.
- For administration of large doses, pool multiple vials using aseptic technique
- Infuse QIVIGY using a separate infusion line. At the end of the infusion flush tubing with saline solution or Dextrose 5% in water (D5W) to ensure that the entire dose is administered.
- Do not mix QIVIGY with other IGIV products or other intravenous medications (including normal saline)
- Do not use after expiration date.
- Record the batch number every time QIVIGY is administered to a patient.
- Dispose partially used or unused product or waste material in accordance with local requirements.

2.3 Administration

Intravenous administration only.

- Hydrate the patient adequately prior to the initiation of infusion.
- Infuse QIVIGY intravenously using an intravenous infusion set. See Table 1 for recommended infusion rates.
- Monitor patient vital signs throughout the infusion.
- The rate of infusion can be related to certain severe adverse drug reactions. Slow or stop infusion if adverse reactions occur.
- If symptoms subside promptly, resume infusion at a lower rate as tolerated by the patient.
- The observation time of patients after QIVIGY administration may vary. If the patient (a) has not received QIVIGY or another IgG product, (b) is switched from an alternative IGIV product or (c) has had a long interval since the previous infusion, prolong the observation time for adverse reactions after QIVIGY infusion.
- Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients at risk of renal dysfunction or thrombosis, administer QIVIGY at the minimum dose and infusion rate practicable and discontinue QIVIGY if renal function deteriorates *[see Boxed Warning, Warnings and Precautions (5.2, 5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

QIVIGY is a liquid, sterile solution for infusion 10% IgG (100 mg/mL), for intravenous infusion in the following presentation:

- 5 g Immune Globulin per 50 mL single dose vial
- 10 g Immune Globulin per 100 mL single dose vial

4 CONTRAINDICATIONS

QIVIGY is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.

QIVIGY is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions, including anaphylaxis, may occur with QIVIGY *[see Adverse Reactions (6)]* In case of hypersensitivity, discontinue QIVIGY infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

QIVIGY contains IgA (≤ 50 mg/L) *[see Description (11)]*. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. QIVIGY is contraindicated in IgA deficient patients with antibodies against IgA and patients with a history of hypersensitivity reaction *[see Contraindications (4)]*.

5.2 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including QIVIGY. 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 those with cryoglobulins, fasting chylomicronemia, high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer QIVIGY at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis *[see Boxed Warning, Dosage and Administration (2)]*.

5.3 Renal Injury

Renal injury including acute renal dysfunction, acute renal failure, acute tubular necrosis, proximal tubular nephropathy, and, osmotic nephrosis may occur after treatment with immune globulin products including QIVIGY. Ensure that patients are not volume depleted prior to the initiation of the infusion of QIVIGY. For patients judged to be at risk for 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 over 65 years), administer QIVIGY at the minimum infusion rate practicable *[see Dosage and Administration (2)]*. The risk of renal dysfunction and acute renal failure is greater in products that contain sucrose, though may still occur in products without sucrose. QIVIGY does not contain sucrose.

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 QIVIGY and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing QIVIGY *[see Dosage and Administration (2)]*.

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, hyperviscosity, and hyponatremia may occur in patients receiving immune globulin treatment, including QIVIGY. 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.

5.5 Aseptic Meningitis Syndrome

Aseptic meningitis syndrome (AMS) may occur in patients following immune globulin treatment, including QIVIGY. The risk of AMS may be higher with high doses (2 g/kg) and/or rapid infusion of immune globulin products. AMS usually begins within several hours to two days following immune globulin treatment and is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. 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 symptoms and signs of AMS, including CSF studies, to rule out other causes of meningitis. Discontinuation of immune globulin treatment has resulted in remission of AMS within several days without sequelae.

5.6 Hemolysis

Hemolysis may occur after administration of immune globulin products, including QIVIGY due to the presence of blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immune globulin, causing a positive direct antiglobulin test and hemolysis. Delayed hemolytic anemia can develop after immune globulin treatment due to enhanced RBC sequestration, and acute hemolysis consistent with intravascular hemolysis has been reported.

The risk factors for hemolysis include high doses (e.g., ≥ 2 g/kg) given either as a single administration or divided over several days, non-O blood group, and an underlying inflammatory disease condition.

Monitor patients for clinical signs and symptoms of hemolysis. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 hours and again 7 to 10 days post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit are observed after QIVIGY infusion, perform confirmatory laboratory testing.

5.7 Transfusion-related Acute Lung Injury

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

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, immediately stop QIVIGY infusion, and perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in both the product and patient's serum. Manage patients using oxygen therapy with adequate ventilatory support as appropriate.

5.8 Transmissible Infectious Agents

There is risk of transmission of infectious disease or agents including viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and the Creutzfeldt-Jakob disease agent with QIVIGY administration because it is manufactured using human blood. The risk of infectious agent transmission is minimized by plasma donor screening, donation testing, and manufacturing steps proven to inactivate and remove bloodborne pathogens.

Any infection suspected to have been transmitted by this product should be reported by the physician or other healthcare provider to **Kedrion Biopharma Inc. at 1-855-3KDRION (1-855-353-7466)**.

5.9 Monitoring Laboratory Tests

- Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of QIVIGY and at appropriate intervals thereafter *[see Warnings and Precautions (5.3)]*.
- 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 (5.2)]*.
- If signs and/or symptoms of hemolysis are present after an infusion of QIVIGY, perform appropriate laboratory testing for confirmation *[see Warnings and Precautions (5.6)]*.
- 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 the administration of immune globulin, the transitory rise of the various passively transferred antibodies in the patients' 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 or indirect antiglobulin test (Coombs test).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The safety data described in this section reflects exposure to QIVIGY in one clinical study. A total of 47 patients with PI received intravenous infusion of QIVIGY at a dose range of 266 to 826 mg/kg every 3 or 4 weeks for up to 12 months *[see Clinical Studies (14)]*. A total of 643 infusions of QIVIGY were administered, 136 in the every 3-week schedule and 507 in the 4-week schedule. During the study, 4 out of 47 (9%) patients received premedication.

The most common product-related adverse events observed in ≥ 5% of clinical study patients with PI were headache, infusion-related reaction, Coombs direct test positive, fatigue, and nausea. Table 2 lists the most common adverse reactions reported in ≥5% of patients.

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

Adverse Reaction	By Patients n (%) [n = 47]	By Infusions n (%) [n = 643]
Headache	14 (30)	26 (4)
Fatigue	7 (15)	10 (2)
Nausea	6 (13)	6 (<1)
Infusion-related Reaction	5 (11)	7 (1)
Coombs Direct Test Positive	5 (11)	8 (1)
Sinusitis	3 (6)	3 (<1)
Dizziness	3 (6)	3 (<1)
Diarrhea	3 (6)	4 (<1)

* Adverse reactions were defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period.

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), Transfusion-Related Acute Lung Injury (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 INTERACTION

7.1 Effect of QIVIGY on Live attenuated virus vaccines

Immune globulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, s and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response. Inform the immunizing physician of recent therapy with QIVIGY so that appropriate measures may be taken.

7.2 Effect of QIVIGY on Serological Testing

Passive transmission of antibodies through immune globulin administration may interfere with some serological testing *[see Warnings and Precautions (5.10)]*.

7.3 Effect of Loop diuretics on QIVIGY

The use of loop diuretics should be avoided. Concomitant use of loop diuretics with IGIV may 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 QIVIGY. It is not known whether QIVIGY can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation. QIVIGY should be given to pregnant women only if clearly needed. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 - 4% and 15 - 20%, respectively.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

The safety and effectiveness of QIVIGY have not been established in pediatric patients.

8.5 Geriatric Use

Seven patients with PI at or over the age of 65 years were included in the clinical study of QIVIGY. Clinical study of QIVIGY did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Use caution when administering QIVIGY to patients aged 65 and over who are at increased risk for renal insufficiency or thrombosis *[see Boxed Warning, Warnings and Precautions (5.2, 5.3)]*. For geriatric patients at risk of thrombosis or acute renal failure, administer QIVIGY at the minimum dose and infusion rate practicable.

10 OVERDOSAGE

Overdosage of QIVIGY may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with renal impairment.

11 DESCRIPTION

QIVIGY (immune globulin intravenous, human-kthm) is a ready-to-use, sterile, non-pyrogenic liquid solution of human immune globulin (IgG) for intravenous administration. QIVIGY is clear or slightly opalescent, colorless or pale yellow. QIVIGY consists of immune globulin of which IgG represents at least 96% of the total protein. It consists of 9 - 11% protein in 0.20 - 0.28 M glycine. In the solution, the IgG proteins are present by more than 97% (at lot release) and 93% (by expiration date) in monomeric and dimeric forms. Minimum value for osmolality is: 240 mOsmol/Kg. pH of the solution is in the range of 4.0 - 4.5. It contains trace levels of IgA (not more than 50 mg/L). The main component of QIVIGY is IgG (≥ 96%) with a sub-class distribution compatible with native human plasma. QIVIGY contains no carbohydrate stabilizers (e.g., sucrose, maltose) and no preservative.

To specifically reduce the anti-A and anti-B titers in the drug product (isoagglutinins A and B), donor plasma is screened for isoagglutinin titer using a validated assay, and plasma units with high agglutination scores are excluded from further processing. All donors of plasma are carefully screened by history and laboratory testing to reduce the risk of transmitting blood-borne pathogens

from infected donors. All plasma units used in the manufacture of QIVIGY are tested and approved for manufacture using FDA-licensed serological assays for Hepatitis B surface antigen (HBsAg), Human immunodeficiency virus 1/2 antibodies (anti-HIV-1/2), and Hepatitis C antibodies (anti-HCV). In addition, donations are screened for Hepatitis C virus (HCV), Human immunodeficiency virus 1 (HIV-1), Hepatitis B virus (HBV), Hepatitis A virus (HAV) and Parvovirus B19 (B19V) by NAT. Further testing is performed on the manufacturing pools for HBsAg and antibodies to HIV-1/2; plasma pools are also tested for HCV, HIV-1, HBV, HAV and B19V by NAT with the limit for B19V set to not exceed 10^4 IU B19V DNA per mL plasma.

QIVIGY is made from large pools of human plasma by a combination of cold alcohol fractionation, caprylate precipitation and filtration, anion-exchange chromatography, nanofiltration and ultrafiltration/diafiltration (UF/DF). QIVIGY is incubated in the final container at the low pH of 4.0 – 4.5. The product is intended for intravenous administration.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by spiking studies at laboratory scale with a validated model of the manufacturing processes, using the following enveloped and non-enveloped viruses: HIV-1 as the relevant virus for HIV-1 and HIV–2; Bovine Viral Diarrhea virus (BVDV) as a model for HCV; Pseudorabies virus (PRV) as a model for large enveloped DNA viruses (e.g., Herpes viruses and HBV); HAV as relevant non-enveloped virus, Encephalomyocarditis virus (EMCV) as a model for HAV, and Porcine Parvovirus (PPV) as a model for human parvovirus B19.

The viral clearance capacity of QIVIGY manufacturing process has been evaluated by summing logarithmic reduction factors from single steps with significant reduction factors more than 1 log, obtaining overall log reduction factors (LRFs) reported in Table 3.

The manufacturing process for QIVIGY includes four steps to reduce the risk of virus transmission. Two of these are dedicated virus clearance steps: sodium caprylate incubation to inactivate enveloped viruses and virus filtration to remove, by size exclusion, both enveloped and non-enveloped viruses as small as approximately 20 nanometers. In addition, caprylate precipitation and filtration step and low pH treatment step contributes to the virus reduction capacity.

Overall virus reduction was calculated only from steps that were orthogonal in mechanisms of removal/inactivation. In addition, each step was verified to provide robust virus reduction across the production range for key operating parameters.

Table 3: Viral Inactivation/Removal Capacity of the QIVIGY Manufacturing

Process	**LRF**	**Enveloped**	**Viruses**	**LRF**	**Non-Enveloped**	**Viruses**
Step	**BVDV**	**HIV-1**	**PsRV**	**HAV**	**PPV**	**EMCV**
1st Caprylate (precipitation+depth filtration)	3.35	NI	NI	> 5.93	2.69	NI
2nd Caprylate (inactivation)	> 5.37	> 4.54	> 6.79	NA	NA	NA
Nanofiltration	> 5.26	2.27	NI[1]	> 4.85	> 6.19	> 4.28
Inactivation by Low pH	2.45	6.17	6.65	NI	NI	3.43
Overall Viral Reduction	**> 16.43**	**> 12.98**	**> 13.44**	**> 10.78**	**> 8.88**	**> 7.71**

NI: not investigated.
NA: Not applicable.
[1]: Due to the low pH condition at which nanofiltration was performed, PsRV was immediately inactivated and it was not possible to properly evaluate virus removal by nanofiltration.

Concerning vCJD risk, donor exclusion criteria are in accordance with the relevant FDA Guidance for Industry (Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Components, current edition).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

QIVIGY is an IgG replacement therapy for primary humoral immunodeficiency. QIVIGY supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against bacterial and, viral agents. The mechanism of action of IgG in PI has not been fully elucidated.

12.2 Pharmacodynamics

QIVIGY contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against various infectious agents reflecting the IgG activity found in the donor population. QIVIGY which is prepared from pooled material from not less than 1000 donors, has an

IgG subclass distribution similar to that of native human plasma. Adequate doses of IGIV can restore abnormally low IgG level to the normal range. Standard pharmacodynamic studies were not performed.

12.3 Pharmacokinetics

In the clinical study assessing the efficacy and safety of QIVIGY in 47 patients with PI [see Clinical Studies (14)], serum concentrations of total IgG were measured in 23 patients following the 5th infusion of QIVIGY for patients on the 4-week dosing schedule, or the 7th infusion for patients on the 3-week dosing schedule. The dose of QIVIGY used in these patients ranged from 266 mg/kg to 826 mg/kg. After infusion, blood samples for PK analyses were collected until Day 21 or Day 28 for patients treated according to the 3-week and 4-week schedule, respectively. Table 4 summarizes the PK parameters of QIVIGY based on serum concentrations of total IgG.

Table 4: Pharmacokinetic Parameters of QIVIGY

Parameter (unit)	3-Week Dosing Interval (n=5) Mean† (CV%)	4-Week Dosing Interval (n=18) Mean† (CV%)
Cmax (mg/dL)	2680 (10.5)	2300 (20.3)
Cmin (mg/dL)	1140 (13.2)	994 (20.2)
Tmax (h)[a]	0.53 (0.5 - 2.02)	0.52 (0.5 - 23.8)
AUC(0-t) (day*mg/dL)	31700 (19.0)	37300 (20.7)
AUCtau (day*mg/dL)	34000 (10.7)	38000 (17.1)
Half-life (day)	24.5 (9.92)	37.3 (30.1)
Clearance (dL/day/kg)	0.019 (15.8)	0.014 (25.5)
Volume of distribution (dL/kg)	0.67 (6.0)	0.70 (16.9)

AUC(0-t) = area under the concentration-time curve from time 0 to the time t of the last quantifiable concentration, AUCtau = area under the concentration versus time curve within a dosing interval, tau = dosing interval, Cmax = maximum observed concentration, Tmax = time at which Cmax was apparent, CV% = coefficient of variation.
[a]: Median and range are presented for t_{max}.
† Arithmetic mean

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

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

13.2 Animal toxicology and/or pharmacology

An acute animal toxicology study was conducted to evaluate possible toxicity of QIVIGY before clinical trial. There were no toxicological concerns for the therapeutic use of QIVIGY.

14 CLINICAL STUDIES

The efficacy of QIVIGY was evaluated in an open-label, prospective clinical study in adult patients with primary humoral immunodeficiency (NCT03961009). A total of 47 patients received intravenous infusion of QIVIGY at the dose of 266 to 826 mg/kg every 3 or 4 weeks for 12 months. Thirty-nine and 8 patients were administered QIVIGY on a 4-week or a 3-week infusion cycle, respectively.

The population characteristics were as follows: The median age was 56 years (range 20 to 70 years), 30 patients (64%) were female, 45 patients (96%) were White, and 2 patients (4%) were of “other” race.

The primary efficacy outcome was the incidence rate of acute serious bacterial infections (SBIs; bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, and osteomyelitis/septic arthritis). Secondary efficacy outcomes included the incidence rate of infections other than acute SBIs, patients hospitalized due to infection, number and duration of antibiotic treatment for any kind of infection, and missed work/school/other major activities due to infections. Table 5 summarizes the efficacy results.

Table 5: Summary of QIVIGY Efficacy Results (N=47)

Efficacy Outcome	Result
Annualized rate of acute SBIs	0 acute SBIs/person-year
Annualized rate of other infections (not including acute SBIs)	2.1 infections per patient year
Patients hospitalized due to infection	0
Antibiotics Number of antibiotics courses Median duration of antibiotic use (min, max)	 113 10 (1, 334) days
Missed work/school/other major activities due to infections Number of patients Median (min, max)	 9 6 (1, 53) days

16 HOW SUPPLIED/STORAGE AND HANDLING

QIVIGY is supplied in single-dose, tamper evident vials containing the labeled amount of functionally active IgG. The vial labels incorporate integrated hangers. The components used in the packaging for QIVIGY are not made with natural rubber latex.

Each product presentation includes a package insert and the components are listed in Table 6.

Table 6: Package Insert and components of QIVIGY presentations

Presentation	NDC Number of Carton	NDC Number of Label
50 mL Vial containing 5 grams of protein	76179-010-01	76179-010-02
100 mL Vial containing 10 grams of protein	76179-010-03	76179-010-04

Storage

Do not use QIVIGY after the expiration date which is stated on the carton and label after "EXP." The expiration date refers to the last day of that month.

Store QIVIGY at 2 °C - 8 °C (36 °F - 46 °F) for up to 36 months.

Keep the vial stored in the outer carton in order to protect from light.

Do not freeze.

17 PATIENT COUNSELING INFORMATION

Discuss the following with the patient.

- Hypersensitivity Reactions: Inform patients that hypersensitivity reactions may occur with QIVIGY infusion. Prior to starting QIVIGY ask about a history of allergic reactions to immune globulin or other blood products. Advise patients to seek immediate medical evaluation if any signs and symptoms of hypersensitivity or acute infusion reactions occur *[see Warnings and precautions (5.1)]*.
- Renal Injury: Inform patients that renal injury may occur with QIVIGY infusion. Advise patients to seek immediate medical evaluation if any signs and symptoms of renal injury occur such as decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath *[see Warnings and Precautions (5.3)]*.
- Thrombosis: Inform patients that thrombosis may occur after QIVIGY infusion. Advise patients to seek immediate medical evaluation if any signs and symptoms of thrombosis occur such as 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, numbness or weakness on one side of the body *[see Warnings and Precautions (5.2)]*

- Aseptic meningitis syndrome (AMS): Inform patients that AMS may occur after QIVIGY infusion. Advise patients to seek immediate medical evaluation if any signs and symptoms of AMS occur such as severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting *[see Warnings and Precautions (5.5)]*
- Hemolysis: Inform patients that hemolysis may occur after QIVIGY infusion. Advise patients to seek immediate medical evaluation if any signs and symptoms of hemolysis occur such as fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine *[see Warnings and Precautions (5.6)]*
- Transfusion-Related Acute Lung Injury (TRALI): Inform patients that TRALI may occur after QIVIGY infusion. Advise patients to seek immediate medical evaluation if any signs and symptoms of TRALI occur such as breathing difficulty, chest pain, blue lips or extremities, and fever *[see Warnings and Precautions (5.7)]*.
- Transmission of Infectious Agents: Inform patients that QIVIGY is a derivative of human plasma and may contain infectious agents that cause disease (e.g., viruses, vCJD agent and, theoretically, CJD agent). Inform patients that the risk that QIVIGY may transmit an infectious agent has been reduced by screening plasma donors for prior exposure for certain viruses, by testing the donated plasma for certain virus infections, and by inactivating and/or removing certain viruses during manufacturing *[see Warnings and Precautions (5.8)]*.
- Drug Interactions: Inform patients that QIVIGY can interfere with their immune response to live virus vaccines such as measles, mumps, varicella and rubella. Inform patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations *[see Drug Interactions (7)]*.

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