PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

HyQvia®

Normal Immunoglobulin (Human) 10% 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL, 30 g/300 mL
and
Recombinant Human Hyaluronidase 200 Units/1.25 mL, 400 Units/2.5 mL, 800 Units/5 mL, 1600 Units/10 mL and 2400 Units/15 mL

Solution for Subcutaneous Infusion

Replacement Therapy for Immunodeficiencies

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RECENT MAJOR LABELS CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

HyQvia is indicated for:

- replacement therapy for primary humoral immunodeficiency (PI) and secondary humoral immunodeficiency (SI) in adult and pediatric patients 2 years of age or older.

- chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with intravenous immunoglobulin (IVIG) to prevent relapse of neuromuscular disability and impairment in adults.

1.1 Pediatrics

Primary and Secondary Humoral Immunodeficiencies

Pediatrics (2 to < 18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of HyQvia in pediatric patients has been established. Therefore, Health Canada has authorized this indication for pediatric use. [see 4 DOSING AND ADMINISTRATION, 4.4 Administration, Patients with a body weight under 40 kg, 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics, 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions - Pediatrics, 14 CLINICAL TRIALS, 14.1 Clinical Trials by Indication, Primary Immunodeficiencies (PI) and Secondary Immunodeficiencies (SI)].

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

No data are available to Health Canada; therefore, Health Canada has not authorized this indication for pediatric use.

1.2 Geriatrics

Primary Immunodeficiency

HyQvia was evaluated in 7 subjects over age 65 in the clinical trial. The available data are too limited to draw safety conclusions (see 4.2 Recommended Dose and Dose Adjustment, 7 WARNINGS AND PRECAUTIONS and 7.1.4 Geriatrics).

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

HyQvia was evaluated in 13 subjects over age 65 in the pivotal trial. The available data are too limited to draw safety conclusions.

Use caution when administering HyQvia to patients 65 years of age or older who are considered to be at increased risk of developing thrombosis and acute renal insufficiency [see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 4 DOSAGE AND ADMISTRATION, 4.2 Recommended Dose and Dose Adjustment, 7 WARNINGS AND PRECAUTIONS and 7.1.4 Geriatrics].

2 CONTRAINDICATIONS

HyQvia is contraindicated in:

- patients with a history of anaphylactic or severe systemic reactions to immunoglobulin G (IgG),
- IgA deficient patients with antibodies to IgA,
- patients with known hypersensitivity to hyaluronidase, including recombinant human hyaluronidase (rHuPH20) of HyQvia,
- patients who are hypersensitive to this drug or to any of the ingredients in the formulation, including any non-medicinal ingredients, or component of the containers. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Thrombotic and thromboembolic events have been reported in association with immunoglobulin products including myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins. Thrombosis may occur even in the absence of known risk factors.
- Thrombosis may occur with immunoglobulin products, including HyQvia. Risk factors for thromboembolic events include: obesity, advanced age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, hypercoagulable conditions, use of estrogens, indwelling central vascular catheters, and cardiovascular risk factors. For further information please refer to 7 WARNINGS AND PRECAUTIONS, Cardiovascular.
- Treating physician should discuss the risk and benefits of this product with the patient. For patients at risk of thrombosis, administer HyQvia 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 of hyperviscosity.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should be commenced and initially monitored under the supervision of a physician experienced in the treatment of immunodeficiency. Patients should be closely monitored and carefully observed for any adverse reactions throughout the infusion period, particularly naïve patients starting therapy.
- The two components of HyQvia must be infused sequentially, beginning with the rHuPH20. The full contents of the rHuPH20 vial should be administered regardless of whether the full content of the immunoglobulin 10 % (IG, 10%) vial is administered. If using two or three infusion sites, divide the rHuPH20 evenly between all infusion sites.

- Use caution when administering HyQvia to patients 65 years of age or older who are considered to be at increased risk of developing thrombosis and acute renal insufficiency [see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 4 DOSAGE AND ADMISTRATION, 4.2 Recommended Dose and Dose Adjustment, 7 WARNINGS AND PRECAUTIONS and 7.1.4 Geriatrics].. Do not exceed the recommended dose, and administer HyQvia at the minimum dose and infusion rate practicable.

4.2 Recommended Dose and Dosage Adjustment

Primary and Secondary Immunodeficiency

Patients naïve to immunoglobulin treatment:

For patients naïve to IgG treatment, administer HyQvia gradually from a weekly equivalent dose to a 3 or 4 week interval at 300 to 800 mg/kg (Table 1). Adjust dosage and treatment interval as necessary based on serum IgG trough levels and infection rates.

Table 1: Example of an Initial Treatment Interval/Dosage Ramp-Up Schedule

Week	Infusion Number	Dose Interval	Proportion of the target dose for a 4-week dosing regimen
1	1st infusion	1-week-dose	25%
2	2nd infusion	2-week-dose	50%
3	No infusion		
4	3rd infusion	3-week-dose	75%
5	No infusion		
6	No infusion		
7	4th infusion (if required)	4-week-dose	100%

Patients previously treated with immunoglobulin administered intravenously:

For patients switching directly from intravenous (IV) administration of immunoglobulin, or who have a previous intravenous dose of immunoglobulin that can be referenced, HyQvia should be administered at the same dose and at the same frequency as their previous intravenous immunoglobulin treatment. When switching from IV treatment begin HyQvia 1 to 2 weeks after the last IV dose. If patients were previously on a 3-week dosing regimen, increasing the interval to 4 weeks can be accomplished by administering the same weekly equivalents.

Patients previously treated with weekly immunoglobulin administered subcutaneously:

For patients currently being administered immunoglobulin subcutaneously, the initial dose of HyQvia is the same as for subcutaneous treatment, but may be adjusted to 3- or 4-week intervals based on the weekly equivalents. The first infusion of HyQvia should be given one week after the last treatment with the previous immunoglobulin.

Pediatric Population

The dosing schedule for children and adolescents (2 to < 18 years) with Primary and Secondary

Humoral Immunodeficiencies is the same as for adults. The dosing is based on body weight and adjusted to the clinical outcome. Refer to Sections 8.2.1 Clinical Trial Adverse Reactions – Pediatrics and 10.3 Pharmacokinetics for description of currently available data.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Patients Treated Previously with Immune Globulin Administered Intravenously (IGIV):

- Patients switching directly from intravenous administration of immune globulin must be on a stable doses of IGIV.
- Before initiating therapy with HyQvia, calculate the weekly equivalent dose by dividing the last IGIV dose by the IGIV dose interval in weeks.
- The starting dose and dosing frequency of HyQvia is the same as the patient's previous IGIV treatment. The typical dosing interval range in the clinical trial for HyQvia was 2 to 4 weeks. For patients with less frequent IGIV dosing (greater than 4 weeks), the dosing interval can be converted to 3 or 4 weeks while maintaining the same monthly equivalent IgG dose.
- Administer the calculated one-week dose (first infusion) two weeks after the last IGIV infusion as directed in Table 2. One week after the first HyQvia dose, administer another weekly equivalent dose (second infusion).
- A dose ramp-up schedule is recommended by gradually increasing the SC infusion volume until the full dose is reached to ensure the patients' tolerability. A ramp-up period can take up to 9 weeks (see Table 1), depending on the dosing interval and tolerability.

The transition and ramp-up schedules for IGIV to HyQvia used in the pivotal trial is provided in Tables 2 and Table 3.

Table 2. IGIV to HyQvia Transition Schedule

IGIV Infusion Schedule	Target HyQvia Schedule	Target HyQvia Dose	Ramp-up Period to Reach Target HyQvia Dose	Number of infusion visits during ramp-up period to reach target HyQvia dose
Every 2 weeks	Every 2 weeks	The same dose as IGIV	4 weeks	3
Every 3 weeks	Every 3 weeks	The same dose as IGIV	6 weeks	4
Every 4 weeks	Every 4 weeks	The same dose as IGIV	9 weeks	5
Every 4 weeks (Accelerated ramp up)	Every 4 weeks	The same dose as IGIV	4 weeks	3

Table 3. IGIV to HyQvia Infusion Dose Ramp-up Schedule

HyQvia Infusion										
IGIV Infusion Schedule	First		Second		Third		Fourth		Fifth	
	Time	Dose	Time	Dose	Time	Dose	Time	Dose	Time	Dose
Every 2 weeks	2 weeks after the last IGIV infusion	Half (1/2) of the dose at the last IGIV infusion	1 week after the first HyQvia infusion	Half (1/2) of the dose at the last IGIV infusion	1 week after the second HyQvia infusion	FULL DOSE REACHED Dose equivalent to the last IGIV infusion	N/A	N/A	N/A	N/A
Every 3 weeks	2 weeks after the last IGIV infusion	One third (1/3) of the dose at the last IGIV infusion	1 week after the first HyQvia infusion	One third (1/3) of the dose at the last IGIV infusion	1 week after the second HyQvia infusion	Two thirds (2/3) of the dose at the last IGIV infusion	2 weeks after the third HyQvia infusion	FULL DOSE REACHED Dose equivalent to the last IGIV infusion	N/A	N/A
Every 4 weeks	2 weeks after the last IGIV dose	Quarter (1/4) of the dose at the last IGIV infusion	1 week after the first HyQvia infusion	Quarter (1/4) of the dose at the last IGIV infusion	1 week after the second HyQvia infusion	Half (1/2) of the dose at the last IGIV infusion	2 weeks after the third HyQvia infusion	Three quarters (3/4) of the dose at the last IGIV infusion	3 weeks after the fourth HyQvia infusion	FULL DOSE REACHED Dose equivalent to the last IGIV infusion
Every 4 weeks (Accelerated ramp up)	2 weeks after the last IGIV dose	Half (1/2) of the dose at the last IGIV infusion	2 weeks after the first HyQvia infusion	Half (1/2) of the dose at the last IGIV infusion	2 weeks after the second HyQvia infusion	FULL DOSE REACHED Dose equivalent to the last IGIV infusion				

Pediatric population:

HyQvia has not been evaluated in clinical studies in children or adolescent patients (0 to 18 years) with CIDP. Health Canada has not authorized this indication for pediatric use.

Elderly patients, patients at increased risk of thrombosis or patients with renal impairment:

Refer to the 4.1 Dosing Considerations section.

Dose Adjustment

For patients at risk for measles exposure:

If a patient has been exposed to measles, please refer to the National Advisory Committee on Immunization (NACI) recommendations[1]for measles post-exposure prophylaxis.

For patients with renal dysfunction or failure:

Lower the dose and the rate of HyQvia infusion (see 7 WARNINGS AND PRECAUTIONS, Renal, Renal Dysfunction/Failure).

For patients with hepatic impairment:

HyQvia has not been evaluated in patients with hepatic impairment.

4.4 Administration

HyQvia should be administered by a healthcare professional, caregiver or self-administered by the patient after training.

- **For subcutaneous administration only. Do not administer HyQvia intravenously.**
- **The two components must be infused sequentially through the same subcutaneous needle, beginning with the rHuPH20 followed by IG 10%.** If using two or three infusion sites, divide the rHuPH20 evenly between all infusion sites.
- Initiate infusion of the full dose of the Immune Globulin Infusion 10% (Human) through the same subcutaneous needle set within approximately 10 minutes of the rHuPH20 infusion. For each full or partial vial of Immune Globulin Infusion 10% (Human) used, administer the entire contents of the rHuPH20 vial.
- Infusion site leakage can occur during or after subcutaneous administration of immunoglobulin, including HyQvia. Consider using longer needles (14 or 12 mm rather than 9 mm) and/or more than one infusion site. Any change of needle size would have to be supervised by the treating physician.
- HyQvia can be administered in a full therapeutic dose at up to 3 infusion sites, up to every 4-weeks. Adjust the frequency and number of infusion sites, considering volume, total infusion time, and tolerability so that the patient receives the same weekly equivalent dose.

Instructions for Preparation and Use

- Visually inspect both components of HyQvia for discoloration and particulate matter prior to administration.
- The appearance of the Immune Globulin Infusion 10% (Human) of HyQvia can vary from clear, colourless to slightly opalescent or pale yellow.
- The appearance of the rHuPH20 of HyQvia should be clear and colorless.
- Do not use either component of HyQvia if either solution is cloudy or has particulates.
- Allow refrigerated product to come to room temperature before use. Do not use heating devices including microwaves.
- Do not shake HyQvia.
- Do not mix the rHuPH20 and the Immune Globulin Infusion 10% (Human) two components of HyQvia into the same container prior to administration.

- See detailed Instructions for Administration in PATIENT MEDICATION INFORMATION.

Infusion Rate

Device-assisted Infusion

Recombinant Human Hyaluronidase (rHuPH20)

The rHuPH20 may be manually infused or infused by a pump. A 24 gauge needle may be required to allow patients to infuse at flow rates of 300 mL/hr/infusion site. However, needles with smaller diameters may be used if slower flow rates are acceptable. For the 1.25 mL size vial of rHuPH20 use an 18-22 gauge needle to withdraw the contents of the vial; for all other vial sizes a needle or needle-less device may be used to withdraw the contents of the vial.

The full dose of rHuPH20 solution (80 Units/0.5mL per gram of IG,10%) is infused at a rate of 1 to 2 mL per minute per infusion site or as tolerated.

Immunoglobulin (IG)

Infuse the dose of IG, 10% through the same subcutaneous needle set within approximately 10 minutes after rHuPH20 infusion is completed. The IG, 10% component should be infused using a pump.

Home-treatment

In case where subcutaneous infusion of HyQvia is used for home treatment, therapy should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. The patient or a caregiver must be instructed on infusion techniques; the use of an infusion pump or syringe driver; the keeping of a treatment diary; recognition of possible severe adverse reactions; and measures to be taken in case these occur.

The following initial infusion rates of IG, 10% are recommended per infusion site (see Table 4).

Table 4: Immunoglobulin, 10% Infusion Rates

	Subjects < 40 kg		**Subjects ≥ 40 kg**	
Interval/Minutes	First Two Infusions (mL/hour/infusion site)	Subsequent 2-3 Infusions (mL/hour/infusion site)	First Two Infusions (mL/hour/infusion site)	Subsequent 2-3 Infusions (mL/hour/infusion site)
10 minutes	5	10	10	10
10 minutes	10	20	30	30
10 minutes	20	40	60	120
10 minutes	40	80	120	240
Remainder of infusion	80	160	240	300

Patients with a body weight of 40 kg or above:

IG, 10% should be infused at an initial rate of 10 mL/hour/infusion site up to 600 mL per site. If well tolerated, the rate of the administration may be increased at intervals of at least 10 minutes to a maximum of 240 mL/hour/infusion site for the initial one or two infusions. For subsequent infusions the rate can be adjusted to a maximum of 300 mL/hour/infusion site.

Patients with a body weight under 40 kg:

IG, 10% should be infused at an initial rate of 5 mL/hour/infusion site up to 300 mL per site. If well tolerated, the rate of the administration may be increased at intervals of at least 10 minutes to a maximum of 80 mL/hour/infusion site for the initial one or two infusions. For subsequent infusions the rate can be adjusted to a maximum of 160 mL/hour/infusion site.

If the patient tolerates the initial infusions at the full dose per site and maximum rate, an increase in the rate of successive infusions may be considered at the discretion of the physician and the patient.

Selection of Infusion Sites

The suggested site(s) for the infusion of HyQvia are the middle to upper abdomen and thighs. If two sites are used, the two infusion sites should be on opposite sides of the body. If using three sites, the sites should be at least 10 cm apart. Avoid bony prominences or areas that are scarred, inflamed, or infected.

Volume per Site

The dose can be administered at 1, 2, or 3 infusion sites. The maximum infusion volume at each infusion site is 600 mL per site (or as tolerated) for patients whose body weight is greater than or equal to 40 kg, and is 300 mL per site (or as tolerated) for patients whose body weight is less than 40 kg.

4.5 Missed Dose

If a patient misses a dose, administer the missed dose as soon as possible and then resume scheduled treatments on the new dosing day.

5 OVERDOSAGE

Consequences of an overdose of HyQvia are not known, though when IG, 10% is given intravenously, overdose may lead to fluid overload and hyperviscosity.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 5: Dosage Forms, Strengths and Composition

Route of Administration	Strength		Non-medicinal Ingredients	Route of Administration	Strength		Non-medicinal Ingredients
	IG, 10%				rHuPH20, 160 Units/mL		
	Volume (mL)	Protein (g)			Volume (mL)	Volume	
Subcutaneous	25	2.5	Glycine, water for injection	Subcutaneous	1.25	200	Calcium chloride, EDTA disodium, human albumin, sodium chloride, sodium phosphate, water for injection
	50	5.0			2.5	400	
	100	10.0			5	800	
	200	20.0			10	1600	
	300	30.0			15	2400	

HyQvia is a dual vial unit consisting of one vial of human normal immune globulin (Immunoglobulin, 10% or IG, 10%) and one vial of recombinant human hyaluronidase (rHuPH20).

Each vial of IG 10% is supplied with the required quantity of rHuPH20 as shown in Table 5 (e.g., 200 U rHuPH20 per 2.5 g IG, 10%). The components of this product are latex free.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

This product is prepared from large pools of human plasma. Thus, there is a possibility it may contain causative agents of viral or other undetermined diseases.

General

Human normal immunoglobulin and human serum albumin (stabilizer of the rHuPH20) are produced from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C (HCV) and for the non-enveloped hepatitis A (HAV) and parvovirus B19 viruses (see 13 PHARMACEUTICAL INFORMATION).

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. All infections thought by a physician to possibly have been transmitted by

this product should be reported by the physician or other healthcare provider to Health Canada (see PATIENT MEDICATION INFORMATION, Reporting Side Effects).

Cardiovascular

Thromboembolic Events

Thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis have been associated with the use of immunoglobulins.

Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. HyQvia should be administered at the minimum dose and at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration of immunoglobulins.

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity should be assessed.

Risk factors for thromboembolic events include: advanced age, use of estrogens, in-dwelling central vascular catheters, history of vascular disease or thrombotic episodes, acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, diseases which increase blood viscosity and cardiovascular risk factors (including obesity, hypertension, diabetes mellitus, history of atherosclerosis and/or impaired cardiac output).

Driving and Operating Machinery

The ability to drive and operate machines may be impaired by some adverse reactions associated with HyQvia, such as headache, nausea and/or vomiting. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

Hematologic

Hemolysis

IG, 10% including HyQvia, contains blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin. This may cause a positive direct antiglobulin test [DAT (Coombs test)]. Delayed hemolytic anemia can develop subsequent to IG, 10% therapy due to enhanced RBC sequestration; acute hemolysis, consistent with intravascular hemolysis, has been reported.

The following risk factors may be related to the development of hemolysis: high doses (e.g., ≥2 grams/kg, single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of hemolysis but its role is uncertain.

Monitor patients for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after HyQvia infusion, perform appropriate confirmatory laboratory testing.

Monitoring and Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield false 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.

Infusions of immune globulin products can lead to false positive readings in assays that depend on detection of ß-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

Neurologic

Aseptic Meningitis Syndrome (AMS)

An aseptic meningitis syndrome (AMS) has been reported to occur in association with immunoglobulin treatment (including IG, 10% administered intravenously and subcutaneously). AMS may occur more frequently in female patients. The syndrome usually begins within several hours to 2 days following immunoglobulin treatment.

AMS is characterized by the following signs and symptoms: 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 mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred milligram/dL, but negative culture results.

Conduct a thorough neurological examination, including CSF studies, on patients exhibiting such signs and symptoms, to rule out other causes of meningitis. Discontinuation of immunoglobulin intravenous treatment has resulted in remission of AMS within several days without sequelae.

Renal

Renal Dysfunction/Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death may occur upon use of immunoglobulin treatment, especially those containing sucrose. HyQvia does not contain sucrose.

Ensure that patients are not volume depleted prior to the initiation of infusion of HyQvia. 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, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs, etc.) monitor renal function and consider lower, more frequent dosing.

Periodic monitoring of renal function and urine output is particularly important in patients predisposed to be at increased risk for developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of HyQvia and again at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of HyQvia.

Reproductive Health: Female and Male Potential

- **Fertility**

The effects of HyQvia on fertility have not been established. Male and female fertility were evaluated in animal studies (see 16 NON-CLINICAL TOXICOLOGY). Exposure to recombinant human hyaluronidase (rHuPh20) at supratherapeutic dose and assessment of anti-rHuPH20 antibodies revealed no effects on male and female fertility.

- **Immunogenicity of Recombinant Human Hyaluronidase (PH20)**

Development of non-neutralizing antibodies to the rHuPh20 component has been reported in patients receiving HyQvia in clinical studies. The potential exists for such antibodies to cross-react with endogenous hyaluronidase PH20, which is known to be expressed in the adult male testes, epididymis, and sperm. It is unknown whether these antibodies may have any clinical significance in humans.

Respiratory

Transfusion-Related Acute Lung Injury (TRALI)

Non-cardiogenic pulmonary edema (TRALI) has been reported in patients following treatment with immunoglobulin products. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically occur within 1 to 6 hours after treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Sensitivity/Resistance

Severe hypersensitivity reactions may occur, even in patients who had tolerated previous treatment with IG. In case of hypersensitivity, discontinue the HyQvia infusion immediately and institute appropriate treatment.

Immunoglobulin (Human) 10% of HyQvia contains trace amount of IgA (average concentration of 37µg/mL). Patients with IgA deficiency or patients with anti-IgA antibodies potentially are at greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Treatment with HyQvia is contraindicated in IgA deficient patients (see 2 CONTRAINDICATIONS).

Hypersensitivity to recombinant human hyaluronidase rHuPH20 may occur, and consists of a wheal with pseudopods appearing within 5 minutes and persisting for 20 to 30 minutes and accompanied by localized itching.

Skin

Spread of Localized Infection

Do not inject HyQvia into or around an infected or acutely inflamed area due to potential risk of spreading a localized infection.

7.1 Special Populations

7.1.1 Pregnant Women

There are limited data available on the use of HyQvia in pregnant women. As immune globulins increasingly cross the placenta from maternal circulation after 30 weeks of gestation, HyQvia should be given to a pregnant woman only if clearly indicated. It is not known whether HyQvia can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Development and reproductive toxicology studies have been conducted with rHuPH20 in mice and rabbits (see 16 NON-CLINICAL TOXICOLOGY). No adverse effects on pregnancy were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to rHuPH20 were transferred to offspring in utero. The effects of antibodies to the rHuPH20 component of HyQvia on the human embryo or on human fetal development are unknown. Animal reproduction studies have not been conducted with IG, 10% component of HyQvia.

7.1.2 Breast-feeding

It is unknown if HyQvia is excreted in human milk. There are limited safety data available on the use of HyQvia in breast-feeding women.

Precaution should be exercised because immunoglobulins can be excreted in human milk. Physicians should balance the potential risks and only prescribe HyQvia if clearly needed.

7.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of HyQvia has been established only in pediatric patients (2 to < 18 years) with Primary Immunodeficiency. Therefore, Health Canada has authorized the primary and secondary humoral immunodeficiencies indications for pediatric use (see 8 ADVERSE REACTIONS, 8.2.1 Pediatrics, 14 CLINICAL TRIALS).

No data are available to Health Canada for the Chronic Inflammatory Demyelinating Polyradiculoneuropathy indication in pediatric patients; therefore, Health Canada has not authorized this indication for pediatric use.

7.1.4 Geriatrics

HyQvia was evaluated in 7 subjects over age 65 in the clinical trial. The available data are too limited to draw safety conclusions. Monitor patients who are at an increased risk for developing renal failure or thrombotic events. Do not exceed the recommended dose, and consider infusing HyQvia at the minimum dose and infusion rate practicable (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 4.2 Recommended Dose and Dose Adjustment).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Primary Immunodeficiency (PID)

The most frequently reported adverse reactions in clinical trials were local reactions. Other very

common adverse reactions observed in > 5% of subjects were nausea, abdominal pain, diarrhea, vomiting, infusion site pain, infusion site erythema, infusion site swelling, infusion site pruritus, asthenic conditions, pyrexia, edema, myalgia, arthralgia, back pain, headache, dizziness, migraine, rash and hypertension. No serious adverse reactions occurred during the HyQvia clinical trials.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The most common adverse reactions observed in >5% of study subjects in clinical studies of HyQvia for CIDP were local reactions, headache, pyrexia, nausea, fatigue, erythema, pruritus, increased lipase, abdominal pain, back pain, and pain in extremity.

8.2 Clinical Trial Adverse Reactions

Primary and Secondary Immunodeficiency

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety profile of HyQvia was evaluated in four clinical studies (160602, 160603, 160902 and 161101) in 124 unique patients with PID receiving 3,202 infusions (see 14 CLINICAL TRIALS). The study demographics and designs are summarized in Table 11. Adverse reactions occurring in patients ≥ 18 years of age are listed in Table 6.

Table 6: Adverse Reactions Reported in greater than 5% of Subjects (≥ 18 Years Old) Under HyQvia Treatment (Studies 160602, 160603, 160902 and 161101)

Adverse Reactions	Number and Rate (%) by Subject N=86	Rate (%) by Infusions[a] N=2314
Gastrointestinal Disorders		
Nausea	25 (29.1)	3.28
Abdominal pain (including abdominal pain upper, abdominal pain lower and abdominal tenderness)	21 (24.4)	1.51
Diarrhea	21 (24.4)	1.47
Vomiting	11 (12.8)	0.52
General Disorders and Administration Site Conditions		
Local reactions	70 (81.4)	26.75
- Infusion site pain (including injection site pain, infusion site discomfort, tenderness, groin pain)	60 (69.8)	13.87
- Infusion site erythema (including injection site erythema)	31 (36.0)	4.88
- Infusion site swelling (including injection site swelling, infusion site edema, local swelling, local edema)	32 (37.2)	3.59
- Infusion site pruritus (including injection site pruritus, vulvovaginal pruritus)	14 (16.3)	2.51
- Gravitational edema/Genital swelling (including genital edema, scrotal swelling, vulvovaginal swelling)	6 (7.0)	0.43
- Infusion site bruising (including infusion site hematoma, infusion site hemorrhage, injection site hematoma)	5 (5.8)	0.30
- Infusion site mass (including injection site mass, nodule)	6 (7.0)	0.26
- Infusion site warmth	5 (5.8)	0.26

Adverse Reactions	Number and Rate (%) by Subject N=86	Rate (%) by Infusions[a] N=2314
Asthenic conditions (including asthenia, fatigue, lethargy, malaise)	27 (31.4)	3.46
Pyrexia	20 (23.3)	1.30
Edema (including edema peripheral, swelling)	13 (15.1)	1.12
Chills	5 (5.8)	0.95
Musculoskeletal and Connective Tissue Disorders		
Myalgia	14 (16.3)	2.33
Arthralgia	16 (18.6)	0.99
Back pain	11 (12.8)	0.65
Pain in extremity	6 (7.0)	0.48
Nervous System Disorders		
Headache	37 (43.0)	3.54
Dizziness	14 (16.3)	1.08
Migraine	10 (11.6)	0.99
Skin and Subcutaneous Tissue Disorders		
Rash (including rash erythematous, rash maculo-papular, rash papular)	9 (10.5)	0.39
Erythema	6 (7.0)	0.30
Vascular Disorders		
Hypertension	11 (12.8)	0.65

[a] Rate per 100 infusions = total number of adverse events divided by total number of infusions multiplied by 100.

Prior to initiation of treatment with HyQvia in the pivotal Study 160603, 87 patients received 365 infusions of immunoglobulin infusion 10% (Human) encompassing 22.2 patient-years. Among the 87 patients treated, 56 (64.4%) experienced 1 or more adverse reactions. Among the 365 intravenous infusions, 158 adverse reactions occurred for a rate per infusion of 0.43.

A total of 1359 infusions of HyQvia were administered during the trial; 230 of these infusions occurred during the ramp-up period and the other 1129 occurred during the observation period. During the observation period, 81 patients received 1129 infusions of HyQvia; of those, 67 (82.7%) experienced one or more adverse reactions. Among the 1129 HyQvia infusions, 456 adverse reactions occurred for a rate per infusion of 0.40. Seven of these adverse reactions were severe, defined as marked impairment of function, can lead to temporary inability to resume normal life pattern, requires prolonged intervention and/or results in sequelae.

Four adult subjects withdrew from the 160603 trial during the efficacy treatment period with HyQvia due to mild to moderate adverse reactions. One child withdrew due to local pain and one due to fever, vomiting, and headaches. Of the four adults, two withdrew due to local pain and swelling, one had moderate swelling that transiently extended from the abdominal infusion site to the genitalia, and one had back injury.

The local adverse reactions are listed by frequency in Table 7. Mild swelling around the infusion site was present in most infusions due to the large volumes infused, but in general was not considered to be an adverse reaction unless it caused discomfort. Among the 234 local adverse reactions, three were severe (infusion site pain, infusion site swelling and infusion site edema that extended from the abdominal infusion site to the genitalia); all were transient and resolved without sequelae. More than 98% of local reactions were either mild (70.5%) or moderate (28.2%) in severity.

Table 7: Most Frequent Local Adverse Reactions Reported in greater than 1% of Infusion During Treatment with HyQvia in Study 160603

Infusion Site Reaction[a]	Number of Reactions (Rate[b]) N=1129	Local Adverse Reactions due to rHuPH20 only
Discomfort/pain	122 (0.108)	37 (0.033)
Erythema	32 (0.031)	0
Swelling/Edema	35 (0.028)	3 (0.003)
Pruritus	22 (0.019)	6 (0.005)

N = Number of infusions.

[a]Causally related adverse events and/or temporally associated adverse events occuring within 72 hours.

[b]Rate=total number of events divided by total number of infusions.

Sixty-six of the 68 subjects who completed Study 160603 enrolled in a prospective, open-label, multicenter extension trial (160902) to assess the long-term safety and tolerability of HyQvia. Sixty-three of 66 subjects enrolled received HyQvia and 3 received IGIV. Of the 63 subjects who received HyQvia, 48 completed the extension trial. The cumulative exposure of HyQvia across the two trials was 188 subject-years and 2959 infusions, and a maximum exposure of 188 weeks or up to approximately 3.5 years. There were no clinically observable changes in the skin or subcutaneous tissue in either the efficacy or extension clinical trials.

During the combined efficacy and extension trials encompassing more than 3 years, the local adverse reaction rate was 2.6 per patient-year. During the first 12-month period (months 1-12), the rate was 3.68 local adverse reactions per patient-year. During the subsequent 12-month period (months 13-24), the rate declined to 2.12 local adverse reactions per-patient year. Finally, during the third 12-month period (months 25-36), the rate further declined to 0.37 local adverse reactions per patient-year.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

The safety of HyQvia was evaluated in 100 unique patients with CIDP in a randomized, placebo-controlled study (161403) and a single-arm, open-label extension study (161505). A total of 3188 infusions (see Table 7) of HyQvia were administered during these 2 studies. The mean duration of exposure was 5.3 months in the HyQvia group and 4.7 months in the placebo group.

In Study 161403, a total of 4 subjects (3.0%) experienced adverse events (AEs) that led to discontinuation from the study: three (3) subjects in the HyQvia group and 1 in the placebo group. The following AEs led to treatment discontinuation each in one subject receiving HyQvia: cerebrovascular accident; infusion site edema and infusion site pain; and nausea and chills.

In Study 161505, a total of 3 subjects (3.8%) experienced AEs that led to discontinuation from the study and 1 subject (1.3%) died prior to the time of the interim analysis. The AEs leading to discontinuation in the 3 subjects included mantle cell lymphoma in 1 subject, muscular weakness and worsening of CIDP in another subject, and abdominal pain in the third subject. The cause of death in the 1 subject was cholangiocarcinoma.

Table 8: Treatment-Emergent Adverse Events Reported in HyQvia CIDP Study 161403 at a Rate of 2% or Higher and with a Higher Incidence Compared to Placebo

System Organ Class/Preferred Term	HyQvia		Placebo	
	Number and Rate (%) by Subject[b] (N = 62[a])	Rate (%) by Infusions[c] (N=598)	Number and Rate (%) by Subject[b] (N = 70[a])	Rate (%) by Infusions[c] (N=644)
Infections and infestations				
Upper respiratory tract infection	3 (4.8)	5 (0.8)	1 (1.4)	1 (0.2)
Influenza	2 (3.2)	2 (0.3)	0	0
Blood and lymphatic system disorders				
Lymphopenia	2 (3.2)	2 (0.3)	0	0
Nervous system disorders				
Headache	8 (12.9)	25 (4.2)	8 (11.4)	17 (2.6)
Dizziness	4 (6.5)	5 (0.8)	1 (1.4)	1 (0.2)
Tremor	2 (3.2)	2 (0.3)	0	0
Vascular disorders				
Hypertension	4 (6.5)	10 (1.7)	1 (1.4)	1 (0.2)
Hypotension	2 (3.2)	3 (0.5)	0	0
Gastrointestinal disorders				
Nausea	7 (11.3)	8 (1.3)	2 (2.9)	2 (0.3)
Abdominal pain	2 (3.2)	2 (0.3)	0	0
Skin and subcutaneous tissue disorders				
Pruritus	5 (8.1)	14 (2.3)	1 (1.4)	1 (0.2)
Erythema	2 (3.2)	5 (0.8)	0	0
Musculoskeletal and connective tissue disorders				
Back pain	4 (6.5)	4 (0.7)	2 (2.9)	3 (0.5)
Arthralgia	3 (4.8)	3 (0.5)	3 (4.3)	8 (1.2)
Pain in extremity	3 (4.8)	10 (1.7)	1 (1.4)	1 (0.2)
General disorders and administration site conditions				
Injection site erythema	7 (11.3)	16 (2.7)	0	0
Pyrexia	7 (11.3)	9 (1.5)	1 (1.4)	1 (0.2)

System Organ Class/Preferred Term	HyQvia		Placebo	
	Number and Rate (%) by Subject[b] (N = 62[a])	Rate (%) by Infusions[c] (N=598)	Number and Rate (%) by Subject[b] (N = 70[a])	Rate (%) by Infusions[c] (N=644)
Fatigue	6 (9.7)	9 (1.5)	2 (2.9)	2 (0.3)
Infusion site erythema	6 (9.7)	20 (3.3)	0	0
Infusion site pain	5 (8.1)	11 (1.8)	2 (2.9)	8 (1.2)
Injection site pain	5 (8.1)	19 (3.2)	2 (2.9)	4 (0.6)
Infusion site oedema	4 (6.5)	24 (4.0)	1 (1.4)	1 (0.2)
Infusion site pruritus	4 (6.5)	6 (1.0)	0	0
Injection site pruritus	4 (6.5)	9 (1.5)	0	0
Infusion site discomfort	3 (4.8)	9 (1.5)	0	0
Injection site oedema	3 (4.8)	6 (1.0)	1 (1.4)	1 (0.2)
Malaise	3 (4.8)	3 (0.5)	0	0
Asthenia	2 (3.2)	2 (0.3)	0	0
Infusion site extravasation	2 (3.2)	2 (0.3)	0	0
Infusion site reaction	2 (3.2)	2 (0.3)	0	0
Injection site paraesthesia	2 (3.2)	5 (0.8)	0	0
Injury, poisoning and procedural complications				
Ligament sprain	2 (3.2)	2 (0.3)	1 (1.4)	1 (0.2)

a N = number of subjects who were dosed at least once.

b Rate by subject = total number of subjects experiencing the AE divided by total number of subjects multiplied by 100.

c Rate by infusions = total number of AEs divided by total number of infusions multiplied by 100.

Blood Pressure Elevation

In Study 161403 (see 14 CLINICAL TRIALS), blood pressure elevation was reported in 4 subjects (6.5%) treated with HyQvia in this study, including 2 subjects with a history of hypertension on antihypertensive medications. Three of the 4 subjects had events which were causally related and/or temporally associated (occurring within 72 hours).

In Study 161505, blood pressure elevation was reported in 5 subjects (6.3%) in this study, including 1 subject with a history of hypertension on antihypertensive medications. One (1) of the 5 subjects had an event which was causally related and/or temporally associated (occurring within 72 hours).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Primary Immunodeficiencies

HyQvia was evaluated in a pivotal efficacy and safety study (Study 161503) of pediatric patients, with a total of 44 subjects (aged 2 to < 16 years of age). Results are from the interim data analysis, where 34 (77.3%) of subjects completed 12 months of participation (one year of observation period) in the study (see 14.1 Trial Design and Study Demographics). The results of Study 161503 indicated similar safety profiles to adults. HyQvia was also evaluated in a pivotal phase 3 study (Study 160603) in 22 patients between 4 and 16 years of age. Results from the study indicated similar safety profiles to adults. Two children withdrew from Study 160603 during the efficacy treatment period with HyQvia. One child withdrew due to local pain and one due to fever, vomiting, and headaches. Two children withdrew from Study 160603 due to celiac disease flare, and infusion site pain. Adverse reactions occurring in greater than 5% of patients 2 to < 16 years of age are listed in Table 9.

Table 9: Adverse Reactions Reported in greater than 5% of Subjects (2 to < 16 Years Old) Under HyQvia Treatment (Studies 160603 and 161503)

Adverse Reactions	Number and Rate (%) by Subject N=66	Rate (%) by Infusions [a] N=1074
Gastrointestinal Disorders		
Vomiting	9 (13.6)	1.5
Abdominal pain (including abdominal pain upper)	5 (7.5)	0.6
Nausea	4 (6.1)	0.6
General Disorders and Administration Site Conditions		
Local reactions		
- Infusion site pain (including injection site pain, infusion site discomfort)	37 (56.3)	7.9
- Infusion site bruising (including injection site discolouration, infusion site discolouration, infusion site hematoma, infusion site extravasation, injection site extravasation)	17 (25.6)	3.2
- Infusion site pruritus (including injection site pruritus)	14 (21.2)	2.3
- Infusion site erythema (including injection site erythema)	13 (19.7)	3.7
- Infusion site swelling (including injection site swelling, infusion site edema)	11 (16.6)	2.7
Asthenic conditions (fatigue, malaise)	9 (13.6)	1.3
Pyrexia	7 (10.6)	1.9
Injury, poisoning and procedural complications		
Infusion related reaction	6 (9.1)	0.7
Nervous system disorders		
Headache	21 (31.8)	6.7

[a] Rate per 100 infusions = total number of adverse events divided by total number of infusions multiplied by 100.

HyQvia was also evaluated in a prospective, Phase 4, multicentre study in 42 pediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy. No new safety concerns were identified. In an extension study (160902) of HyQvia in 11 patients between 4 and 16 years of age, the results of indicated similar safety profiles to adults.

8.3 Less Common Clinical Trial Adverse Reactions

Blood and Lymphatic System Disorders: haemolysis
General Disorders and Administration Site Conditions: application site erythema, infusion site haemorrhage, infusion site hypersensitivity, infusion site paraesthesia
Immune System Disorders: anaphylactic reaction
Nervous System Disorders: cerebrovascular accident
Vascular disorders: hypotension, thrombosis

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Cardiac Disorders: tachycardia
General Disorders and Administration Site Conditions: chills, infusion site haemorrhage, infusion site hypersensitivity, infusion site inflammation, infusion site nodule and injection site nodule, peripheral swelling
Immune System Disorders: drug hypersensitivity and hypersensitivity
Musculoskeletal and Connective Tissue Disorders: musculoskeletal chest pain
Nervous system disorders: paraesthesia
Respiratory, Thoracic and Mediastinal Disorders: dyspnoea
Skin and Subcutaneous Tissue Disorders: erythema, urticaria
Vascular disorders: blood pressure decreased and hypotension, blood pressure increased, blood pressure systolic increased, hypertension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

No clinically significant changes in laboratory findings have been identified during clinical trials.

8.5 Post-Market Adverse Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience.

Cardiac disorders: Tachycardia
Gastrointestinal Disorders: Paresthesia oral
General Disorders and Administration Site Conditions: Influenza like illness, Infusion site extravasation, Infusion site reactions, Injection site rash, Injection site urticaria, Swelling face
Immune System Disorders: Hypersensitivity, Anaphylactic Shock, Anaphylactic Reaction, Anaphylactoid Reaction
Infections And Infestations: Meningitis aseptic
Investigations: Alanine aminotransferase increased
Musculoskeletal and Connective Tissue Disorders: Musculoskeletal stiffness
Nervous System Disorders: Tremor
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea
Skin and Subcutaneous Tissue Disorders: Dermatitis allergic
Vascular Disorders: Flushing, Hypotension, Pallor, Peripheral coldness

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Antibodies in immunoglobulin preparations may interfere with patient responses to live vaccines, such as those for measles, mumps, rubella, and varicella.

Admixtures of HyQvia with other drugs solutions have not been evaluated. Do not mix or administer components of HyQvia with other products.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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

Infusions of immunoglobulin products may lead to false positive readings in assays that depend on detection of ß-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The human normal immunoglobulin (IG, 10%) provides the therapeutic effect of HyQvia. The recombinant human hyaluronidase PH20 (rHuPH20) facilitates the dispersion and absorption of IG, 10%.

Human normal IG, 10% contains mainly immunoglobulin G (IgG) with a broad spectrum of opsonizing and neutralizing antibodies against a wide variety of bacterial and viral agents. IG, 10% also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these

antibodies and the mechanism of action of IgG in the IG, 10% of HyQvia have not been fully elucidated.

The rHuPH20 is a soluble recombinant form of human hyaluronidase PH20 that modifies the permeability of connective tissue through the hydrolysis of hyaluronan.

Hyaluronan is a polysaccharide found in the intercellular matrix of the connective tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a very fast turnover with half-life of approximately 0.5 days. The rHuPH20 increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. The rHuPH20 of HyQvia acts locally.

The effects of the hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

10.2 Pharmacodynamics

Human normal IG contains the IgG antibodies as well as IgA and trace amounts of IgM, present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

10.3 Pharmacokinetics

Treatment of Primary Immunodeficiency

The pharmacokinetics of subcutaneous HyQvia was evaluated during the clinical study 160603 in patients with PID (aged 12 years and older) after they achieved steady state at their 3 or 4 week dosing interval and underwent individual dose adjustment. Adjustment of dose was based on comparison of the ratios of the area under the IgG concentration versus time curve (AUC) during intravenous treatment versus HyQvia treatment. The pharmacokinetic results are presented in Table 10, as compared to data for intravenous administration of IG, 10% (IVIG) obtained in the same study.

Table 10: Pharmacokinetic Parameters of Subcutaneous HyQvia Compared to Intravenous Administration of IG, 10% in Subjects 12 Years and Older at 3 or 4 week Dosing Interval

Parameter	HyQvia N=60	IVIG, 10% N=68
IgG Weekly Dose [mg/kg/week]		
Mean (SD)	147 (50)	139 (55)
95% CI	134 to 160	126 to 153
C_{max} [mg/dL]		
Mean (SD)	1607 (382)	2248 (547)
95% CI	1508 to 1706	2116 to 2380
IgG Trough Levels [mg/dL][a]		
Mean (SD)	1077 (272)	1095 (321)
95% CI	1004 to 1149	1017 to 1174
AUC per week [g*days/L][b]		
Mean (SD)	91.4 (21)	98.7 (24.3)
95% CI	85.9 to 96.8	92.8 to 104.5
Bioavailability[c]		
Point estimate	93.3	100% defined
90% CI	91.4 to 95.2	N/A
T_{max} [days]		
Median	5.0	0.1
95% CI	3.3 to 5.1	0.1 to 0.1
Clearance [mL/kg/day]		
Mean (SD)	1.6 (0.5)[d]	1.4 (0.4)
95% CI	1.5 to 1.8	1.3 to 1.5
Terminal half-life [days]		
Mean (SD)	59.3 (36.1)	41.6 (26.9)
95% CI	50 to 68.6	35.1 to 48.1

[a] N=58 for HyQvia and N=67 for IVIG
[b] Standardized to a 7 day interval
[c] N=58 HyQvia
[d] Apparent clearance

Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

The pharmacokinetic profile of HyQvia was not evaluated in adult patients with CIDP (Study 161403). Serum trough levels of total IgG were assessed throughout the study.

Pharmacokinetic parameters

Absorption:

In PID patients, HyQvia has a median (range) T_{max} of 5.0 (3.3-5.1) days. The bioavailability of HyQvia based on weekly AUC is 93.3% relative to IGIV in these patients.

Distribution:

The distribution of HyQvia has not been characterized in a dedicated clinical study. HyQvia is expected to be distributed within the vascular space similar to other immunoglobulins.

Metabolism:

The IgG component of HyQvia undergoes catabolism similar to other immunoglobulins.

Excretion:

In PID patients, HyQvia has a mean (SD) terminal half-life of 59.3 (36.1) days and mean (SD) apparent clearance of 1.6 (0.5) mL/kg/day.

Special Populations and Conditions

Pediatrics: Results from the pivotal pediatric study (161503) suggest no clinically meaningful differences across age (2 to 16 years) groups with respect to total IgG PK (AUC/week and CL/F/BW) and serum trough levels. The calculated PK parameters were similar across age groups and consistent with reported parameters from previous clinical studies in subjects 12 years of age and older (see Table 11).

Table 11. Mean (SD) Pharmacokinetic Parameters for Serum Total IgG Following Treatment with HYQVIA in Pediatric Patients Compared to Adults

	Age Group				
Parameter (unit)	2 to < 6 Years Study 161503 (N=7)	6 to <12 Years Study 161503 (N=20)	12 to <16 Years Study 161503 (N=11)	12 to <16 Years Study 160603 (N=9)	Adult, Aged ≥16 Years Study 160603 (N=51)
AUC/week (g•day/L)	69.54 (21.456)	77.59 (9.6537)[b]	76.31 (7.5261)	99.07 (14.497)	90.00 (21.814)
C_{max} (g/L)	12.53 (3.0104)	13.17 (1.6711)	13.09 (1.9897)	17.12 (3.2139)	15.89 (3.9123)
T_{max} (day)[a]	5.22 (2.2, 12.22)	5.08 (2.1, 26.9)	4.07 (2.0, 7.8)	3.05 (2.6, 13.8)	4.98 (1.22, 14.95)
C_{min} (g/L)	7.840 (3.1232)	9.190 (1.5014)	8.710 (1.0904)	11.51 (1.6414)	10.15 (2.6637)
$t_{1/2}$ (day)	42.16 (25.471)[d]	57.10 (33.209)[e]	40.95 (7.6597)[d]	80.229 (58.550)	55.63 (29.887)
CL/F/BW (mL/day/kg)	2.165 (1.2206)	1.749 (0.45038)[b]	1.615 (0.34000)	1.270 (0.2575)	1.693 (0.48906)

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator 2°C to 8°C.

Do not return HyQvia to the refrigerator after it has been stored at room temperature (up to 25°C). HyQvia must be used within 3 months after removal to room temperature.

Do not freeze. Keep the vials in the outer carton in order to protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

Do not shake.

HyQvia should be brought to room temperature before use. Do not use heating devices including microwaves.

The use of a vented vial access device to remove rHuPH20 from vials is not recommended.

Do not use if particulate matter and/or discoloration is observed.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Normal Immunoglobulin (Human)

Chemical name: Human immunoglobulin G

Molecular formula and molecular mass: N/A

Structural formula: The active ingredient of HyQvia is human polyvalent immunoglobulin G (IgG). Immunoglobulins are made up of four polypeptide chains, comprising two identical light chains of a molecular weight of approximately 25 kD and two identical heavy chains of a molecular weight of approximately 50 kD. The four chains form a three-dimensional Y-shaped structure as shown by X-ray crystallography. Carbohydrate groups are attached covalently at distinct positions of the heavy chains. The overall molecular mass of IgG molecules approximates 150 kD.

Each of the four chains has a variable region at the amino-terminus, which contributes to the antigen-binding site, and a constant region. The constant region of the heavy chains determines the isotype (heavy chain class) of the antibody. Variable and constant regions are divided into a series of homologous domains with similar amino acid sequences that each fold into a distinct globular structure.

The light chains are bonded to the heavy chains by non-covalent associations and by disulfide bonds. Variable regions of light and heavy chains pair to generate two identical antigen-binding sites, which lie at the N-termini of the arms of the Y (in the Fab region) and confer specificity to the antibody. The trunk of the Y, or Fc fragment (fragment crystallizable), is composed of the two carboxy-terminal domains of the two heavy chains. Flexible hinge regions join the Fab and Fc parts of the immunoglobulin. The Fc fragment and hinge regions differ in antibodies of different isotypes, thus determining their functional properties.

Immunoglobulin G is the most common immunoglobulin class, with a level of 9-12 g per liter of plasma, accounting for about 75 % of the total immunoglobulins in plasma of healthy individuals. Immunoglobulin G is further divided into subclasses with different heavy chain isotypes: IgG1, IgG2, IgG3 and IgG4.

In the human normal immunoglobulin manufacturing process, the native structure of IgG antibodies, as well as the broad antibody diversity and the IgG subclass distribution are maintained during the enrichment of IgG from human plasma.

Product Characteristics:

HyQvia is supplied in a dual vial unit of two single use vials containing the labeled amount of functionally active IG, 10% and rHuPH20.

<u>Immunoglobulin Infusion (Human)</u>

The Immunoglobulin Infusion (Human), 10% of HyQvia contains a broad spectrum of immunoglobulin G (IgG) antibodies against bacterial and viral agents. Glycine (0.25M) serves as a stabilizing and buffering agent. Trace amounts of sodium are present and there is no added sugar or preservatives. The pH is 4.6 to 5.1. The osmolality is 240 to 300 mOsmol/kg. The maximum

immunoglobulin A (IgA) content is 140 mcg/mL, the average immunoglobulin A (IgA) is approximately 37 mcg/mL, and immunoglobulin M (IgM) is present in trace amounts.

Recombinant Human Hyaluronidase (rHuPH20)

The recombinant human hyaluronidase of HyQvia is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase PH20. The purified hyaluronidase glycoprotein contains 447 amino acids with an apparent molecular weight of 60,000 to 65,000 Daltons. The final formulation has a pH of 6.5 to 8.0 and an osmolality of 290 to 350 mOsmol. Each vial contains 160 U/mL of Recombinant Human Hyaluronidase with 8.5 mg/mL sodium chloride, 1.78 mg/mL sodium phosphate dibasic dihydrate, 1.0 mg/mL human albumin, 1.0 mg/mL edetate disodium dihydrate, 0.40 mg/mL calcium chloride dihydrate, and 0.17 mg/mL sodium hydroxide added for pH adjustment. Recombinant Human Hyaluronidase does not contain preservatives.

Viral Inactivation

The Immunoglobulin Infusion 10% (Human) of HyQvia is manufactured from large pools of human plasma. IgG preparations are purified from plasma pools using a modified Cohn-Oncley cold ethanol fractionation process, as well as cation and anion exchange chromatography.

Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and plasma preparation. Each individual plasma donation used in the manufacture of the Immunoglobulin Infusion 10% (Human) of HyQvia is collected only at FDA approved blood establishments and is tested by FDA licensed serological tests for Hepatitis B Surface Antigen (HBsAg), and for antibodies to Human Immunodeficiency Virus (HIV-1/HIV-2) and Hepatitis C Virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, mini- pools of the plasma are tested for the presence of HIV-1 and HCV by FDA licensed Nucleic Acid Testing (NAT).

To further improve the margin of safety, three dedicated, independent and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent (S/D) treatment, 35 nm nanofiltration, and a low pH incubation at elevated temperature. The S/D process includes treatment with an organic mixture of trin-butyl phosphate, octoxynol 9 and polysorbate 80 at 18°C to 25°C for a minimum of 60 minutes.

In vitro virus spiking studies have been used to validate the capability of the manufacturing process to inactivate and remove viruses. To establish the minimum applicable virus clearance capacity of the manufacturing process, these virus clearance studies were performed under extreme conditions (e.g., at minimum S/D concentrations, incubation time and temperature for the S/D treatment). Virus clearance studies for the Immunoglobulin Infusion 10% (Human) of HyQvia performed in accordance with good laboratory practices (Table 12) have demonstrated that:

- S/D treatment inactivates the lipid-enveloped viruses investigated to below detection limits within minutes.
- 35 nm nanofiltration removes lipid-enveloped viruses to below detection limits and reduces the non-lipid enveloped viruses HAV and B19V. As determined by a polymerase chain reaction assay, nanofiltration reduced B19V by a mean log10 reduction factor of 4.8 genome equivalents.

- Treatment with low pH at elevated temperature of 30°C to 32°C inactivates lipid-enveloped viruses and encephalomyocarditis virus (EMCV, model for HAV) to below detection limits, and reduces mice minute virus (MMV, model for B19V).

Table 12: Three Dedicated Independent Virus Inactivation/Removal Steps Mean Log10 Reduction Factors * (RFs) For Each Virus and Manufacturing Step

Virus Type	**Enveloped RNA**			**Enveloped DNA**	**Non-enveloped RNA**		**Non-enveloped DNA**
Family	**Retroviridae**	**Flaviviridae**		**Herpes viridae**	**Piconarviridae**		**Parvoviridae**
Virus	**HIV-1**	**BVDV**	**WNV**	**PRV**	**HAV**	**EMCV**	**MMV**
SD treatment	> 4.5	> 6.2	n.a.	> 4.8	n.d.	n.d.	n.d
35 nm nanofiltration	> 4.5	> 5.1	> 6.2	> 5.6	5.7	1.4	2.0
Low pH treatment	> 5.8	> 5.5	> 6.0	> 6.5	n.d. †	> 6.3	3.1
Overall log reduction factor (ORF)	> 14.8	> 16.8	> 12.2	> 16.9	5.7 †	> 7.7	5.1

Abbreviations: HIV-1, Human Immunodeficiency Virus Type 1; BVDV, Bovine Viral Diarrhea Virus (model for Hepatitis C Virus and other lipid enveloped RNA viruses); WNV, West Nile Virus; PRV, Pseudorabies Virus (model for lipid enveloped DNA viruses, including Hepatitis B Virus); EMCV, Encephalomyocarditis Virus (model for non-lipid enveloped RNA viruses, including Hepatitis A virus [HAV]); MMV, Mice Minute Virus (model for non-lipid enveloped DNA viruses, including B19 virus [B19V]); n.d. (not done), n.a. (not applicable).

* For the calculation of these RF data from virus clearance study reports, applicable manufacturing conditions were used. Log10 RFs on the order of 4 or more are considered effective for virus clearance in accordance with the Committee for Medicinal Products for Human Use (CHMP, formerly CPMP) guidelines.

† No RF obtained due to immediate neutralization of HAV by the anti- HAV antibodies present in the product.

Due to comprehensive virus testing at the Master Cell Bank, Working Cell Bank and bulk harvest stage, effective virus reduction during the manufacturing process (solvent detergent treatment, purification, and nanofiltraton steps), and use of pharmaceutical grade human albumin as an excipient with no other materials of human or animal origin involved in the manufacturing process, Recombinant Human Hyaluronidase provides for high margins of safety with respect to viruses.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Primary humoral immunodeficiency (PI) and Secondary humoral immunodeficiency (SI)

HyQvia has been evaluated in six clinical trials (160602, 161101, 160603, 160902, 161503 and 161504) in patients with PID. Subjects ranged in age from 4-80 years old with similar numbers of male and female patients in each study.

Table 13: Summary of patient demographics for clinical trials in Primary Immunodeficiency (PI)

Study #	Study design	HyQvia dosage, treatment intervals, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
161101	Prospective, open-label, non-randomized, multi-center study	IGSC, 10% at 100% (± 5%) of pre-study treatment dose given SC every 3 or 4 weeks rHuPH20 was given SC prior to infusions with IGSC, 10% at a dose of 75 U/g IgG	37	33.0 (6-69)	Male: 16 Female: 21
160603	Prospective, open-label, non-randomized, multi-center study	IGI, 10% at pre-study dose given IV every 3 or 4 weeks IGSC, 10% at 108% of IV dose given SC every 3 or 4 weeks rHuPH20 was given SC prior to infusions with IGSC, 10% at a dose of 75 U/g IgG	87	35.0 (4-78)	Male: 44 Female: 43
160902	Prospective, open-label, non-randomized, multi-center study	IGSC, 10% given SC every 2, 3 or 4 weeks rHuPH20 was given SC prior to infusions with IGSC, 10% at a dose of 75 U/g IgG	66	43.0 (9-80)	Male: 34 Female: 32
160602	Prospective, open-label, non-randomized, multi-center study	Dose-escalation: IGSC, 10% at pre-study dose, adjusted to a maximum of 600 mg/kg BW (in a single infusion site) every 4 weeks given SC rHuPH20 was given SC prior to infusions with IGSC, 10%, adjusted based on IGI dose	11	44 (female) 50 (male) (20-76)	Male: 7 Female: 4

Study #	Study design	HyQvia dosage, treatment intervals, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
161503	Pivotal, prospective, non-controlled, multi-center phase 3 study	Epoch 1 (ramp-up) IGSC, 10%: equivalent to 100% (±5%) of the subject's previous dose rHuPH20: dose ratio of approximately 80 U/g IgG before the infusion of IGSC, 10% Epoch 2 IGSC, 10%: 100% (±5%) of the subject's previous dose every 3 or 4 weeks, depending on the subject's previous IV dosing schedule (for IV-pretreated subjects) and at the discretion of the investigator and subject (for SC-pretreated subjects). rHuPH20: dose ratio of approximately 80 U/g IgG before the infusion of IGSC, 10%	44	9.5 (3-15)	M: 26 F: 18
161504	Prospective, non-controlled, multi-centre phase 4 study	Epoch 1 (ramp-up) IGSC, 10%: equivalent to 100% (±5%) of the subject's previous dose rHuPH20: dose ratio of approximately 80 U/g IgG before the infusion of IGSC, 10% Epoch 2 IGSC, 10%: 100% (±5%) of the subject's previous dose every 3 or 4 weeks, depending on the subject's previous IV dosing schedule (for IV-pretreated subjects) and at the discretion of the investigator and subject (for SC-pretreated subjects). rHuPH20: dose ratio of approximately 80 U/g IgG before the infusion of IGSC, 10%	42	11.5 (3-17)	M: 34 F: 8

<u>Study 160603 (Efficacy trial – adults, children, adolescents)</u>

A prospective, open-label, non-controlled, multi-center trial was conducted in the US and Canada to determine the efficacy, tolerability and pharmacokinetics (PK) of HyQvia in subjects with PID. Two cohorts of subjects were enrolled. The median age was 35.0 years (range 4 to 78 years); the majority of subjects (79/87; 90.8%) were White; 2 (2.3%) were Black/African American, 3 (3.4%) were Asian, 1 (1.1%) was American Indian or Alaskan Native, and 2 (2.3%) were of multiple race. With respect to ethnicity, 8/87 (9.2%) of subjects were Hispanic or Latino. The median height and weight were 165.0 cm (range: 94.0-193.0 cm) and 63.8 kg (range: 15.0-135.9 kg), respectively.

Thirty-one subjects had been treated intravenously for three months and then administered subcutaneously each week at 137% of the intravenous dose for approximately one year before transitioning to Study 160603. The remaining subjects also were treated intravenously for 3 months and then immediately began treatment with HyQvia in the trial. Forty-four of the subjects were naïve to subcutaneous treatment.

Median serum IgG trough levels for the 6 months before enrollment were 1033.5 mg/dL (range: 405 to 3200 mg/dL) in subcutaneous-experienced subjects and 1000 mg/dL (range: 636 to 3200) in the subcutaneous-naïve subjects.

One week after the last intravenous or subcutaneous infusion, each subject began subcutaneous treatment with HyQvia. After placing the subcutaneous needle set, the Recombinant Human Hyaluronidase of HyQvia was infused through the needle set followed within 10 minutes by the immunoglobulin of HyQvia at 108% of the intravenous dose. Dosing began with a 1-week equivalent dose. One week later, a 2-week dose was administered, followed 2 weeks later with a 3-week dose. For those subjects who were on a 4-week dose interval prior to entering the trial, they were initiated at 3 weeks followed by 4-week administration interval. This ramp-up period allowed subjects to become familiar with the large volumes required for a full 3- or 4-week treatment. Subsequently, subjects continued the 3- or 4-week dosing for the remainder of the trial. After 3 doses at the full volume, a serum IgG trough level was obtained for all subjects and used to individually adapt the subcutaneous dose of HyQvia to compensate for individual variation from the mean value of 108%. All subjects who completed the trial received a minimum of 12 infusions at this individually adapted dose. The period after the ramp-up was considered the efficacy period and used for safety and efficacy analyses.

Outcome measures included the rate of infections, adverse reactions, tolerability of the infusions of HyQvia, number of infusion sites per month, and infusion rate. Eighty-nine subjects were enrolled, 87 treated intravenously and 83 treated with HyQvia. The majority were Caucasian (79/87, 90.8%).

<u>161503 (Efficacy Trial – children and adolescents)</u>

HyQvia was evaluated in a pivotal, prospective, multi-center phase 3 study in a total of 44 pediatric subjects (aged 2 to 16 years of age). The purpose of this study was to assess the efficacy, safety, tolerability, immunogenicity, and PK, of HYQVIA treatment in pediatric subjects who had received prior IV or SC immunoglobulin therapy, further supporting the administration of HyQvia in pediatric subjects. The study comprised of 3 treatment phases, or Epochs. Eligible subjects were to be treated with HyQvia in Epoch 1 and Epoch 2, administered as SC infusions. Epoch 3 is a 1-year safety-follow up phase. Pediatric subjects switched to HyQvia SC immunoglobulin treatment schedule administered at doses (volumes and treatment intervals) typical for IVIG administration. Treatment intervals and doses in Epoch 1 were gradually increased in a ramp-up phase to an interval of 3 or 4 weeks. Interim data were analyzed and 34 (77.3%) subjects were observed for at least 12 months, while 10 (22.7%) of subjects discontinued the study before their 12-month visit.

<u>Study 160603 adults, children, adolescents:</u>

The 83 subjects received a total of 1359 infusions of HyQvia during the entire trial. Of these, 1129 were administered after the ramp-up when the subjects were on a consistent interval of 3 or 4 weeks, which was predetermined to be the efficacy period for data analysis.

Median duration of treatment in the IGIV period was 91 days (range 84 to 122 days). Median

duration of HyQvia treatment during the dose ramp up period was 42 days (range 20 to 49), and during the efficacy period was 366 days (range 42 to 507 days). None of the subjects withdrew due to a severe or serious local or systemic adverse reaction.

Study Results

There were two acute serious bacterial infections (ASBI), both of which were episodes of pneumonia treated as outpatients with oral antibiotics during the 12-month efficacy period; an additional pneumonia requiring hospitalization occurred during the ramp-up. Based on this, the annualized rate of ASBI while treated with HyQvia was 0.025, with an upper 99% confidence limit of 0.046, which is significantly less than ($p < 0.0001$) the rate of one infection per year.

The overall rates of infections throughout both the efficacy and extension trials are shown in Table 1. The secondary endpoints evaluated in the efficacy trial were the annual rate of all infections and other efficacy measures.

Table 14: Summary of Infections and Other Secondary Efficacy Endpoints

	Annual Rate	
Parameter	**Mean**	**95% CI**
Infections per patient per year (Efficacy Trial)	2.97	2.51 to 3.47
Infections per patient per year (Efficacy and Extension Trials)	2.99	2.60 to 3.92
Days off school/work	3.41	2.44 to 4.5
Days on antibiotics	20.58	15.71 to 26.3
Unscheduled physician visits for infections	4.87	3.9 to 5.97
Days in hospital due to infection	0.0	0.0 to 0.12

An objective of the trial was to achieve the same number or fewer infusions with HyQvia per month as with intravenous administration and significantly fewer than with conventional subcutaneous administration. A summary of intravenous administration compared with HyQvia administration is presented in Table 15.

Table 15: Summary of Infusions

Parameter	**Intravenous**	**HyQvia**
Median monthly number of infusion sites	1.34 (1.2 to 1.7)	1.09 (1.0 to 3.5)
Mean volume per site (mL)	339 (75 to 800)	292 (91 to 648)
Dose per site (g)	33.9 (7.5 to 80.0)	29.2 (9.1 to 64.8)
Median duration of individual infusions (hr)	2.33 (0.92 to	2.08

	6.33)	(0.83 to 4.68)
Monthly median infusion time (hr/month)	3.2	2.64
Median maximum infusion rate (mL/hr)	246 (60 to 668)	300 (10 to 300)
Percent (%) of infusion completed without change in rate, interruption and discontinuation	95.9	97.7

Sixteen of 83 subjects (19.3%) were infused every 3 weeks and 67 (80.7%) were infused every 4 weeks. Seventy-eight of 83 (94%) subjects attained the same 3- or 4-week dosing as their previous IV treatment. One decreased from 4 to 3 weeks, one from 4 to 2 weeks and one from 3 to 2 weeks. The primary reason for decreasing the interval was discomfort due to swelling.

Study 161503 – children and adolescents

HyQvia was shown to be efficacious with respect to the occurrence of Acute Serious Bacterial Infections (ASBIs). Out of 44 subjects, only one subject (2.3%) reported 2 ASBIs of bacterial pneumonia. The mean rate of ASBIs per subject-year was 0.04 and was statistically significantly lower ($p<0.001$) than the threshold rate of 1.0 ASBI per subject-year favoring efficacy of HyQvia treatment in pediatric subjects with PI. The mean rate of all infections per subject-year was 3.20, with an upper limit of the 95% CI of 4.05. Overall, the median number of infusions per month was 1.10 (range: 1.0 to 1.5) and were comparable across the age groups. The median number of infusion sites per month was 2.17 (range: 1.1 to 2.9), with a similar median number of infusion sites per month for all the age categories.

There were no clinically meaningful differences in trough IgG levels across age groups (Table 16).

Table 16: Mean (SD) Serum Total IgG Trough Level Following Treatment with HYQVIA in Pediatric Patients

		Mean (SD) (g/L)		
Age Group	**Statistic**	**Month 0 (Baseline)**	**Month 6**	**Month 12**
2 to <6 years	n	9	8	8
	Mean (SD)	9.43 (2.80)	8.70 (3.30)	9.04 (3.15)
6 to <12 years	n	19	19	20
	Mean (SD)	10.06 (2.48)	9.00 (1.34)	9.35 (1.37)
12 to <16 years	n	12	6	8
	Mean (SD)	10.79 (3.95)	10.10 (0.51)	9.05 (2.11)

SD = Standard deviation

Additionally, a prospective, Phase 4, multicentre study (Study 161504) in Europe evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PID.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Table 17: Summary of patient demographics for clinical trials in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Study #	Study design	HyQvia dosage, treatment intervals, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
161403 (ADVANCE-1)	Epoch 1: Phase 3, prospective, double-blind, placebo-controlled, multicenter study	IGSC, 10% at 100% of pre-study IGIV treatment dose given SC every 2,3 or 4 weeks. rHuPH20 was given SC prior to infusions with IGSC, 10% at a dose of 80 U/g IgG	132	56.0 (19-86)	Male: 74 Female: 58
	Epoch 2: Phase 3, prospective, open-label, multicenter study	IGIV, 10% at 2g/kg BW over 2 to 5 consecutive days, followed by IGIV 10% at pre-study treatment dose every 3 weeks for a period of 6 months.	21 of 132		

In a multicenter, randomized, placebo-controlled, phase 3 study, 132 adult subjects with CIDP underwent evaluation of the efficacy, safety, and tolerability of HyQvia as a maintenance therapy to prevent relapse that allows self-infusion of a total therapeutic dose every 2 to 4 weeks. The study enrolled subjects ≥18 years of age (male or female) at the time of screening who had a documented diagnosis of definite or probable CIDP as per the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria. All eligible subjects had responded to IgG treatment in the past (partial or complete resolution of neurological symptoms and deficits) and were on a stable dose of IGIV treatment within the dose range equivalent to a cumulative monthly dose of 400 to 2400 mg/kg body weight administered intravenously for at least 12 weeks before screening. The primary endpoint was the proportion of subjects who experienced a relapse, defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted inflammatory neuropathy cause and treatment (INCAT) disability scores obtained less than seven days apart. Overall, a total of 184 subjects were screened, of 138 (75%) were randomized, and 132 (71.7%) were dosed with either HyQvia (n=62) or placebo (n=70), 94 (71.2%) randomized patients completed Epoch 1 phase of the study without developing a relapse, and 21 rolled over to Epoch 2.

The mean monthly equivalent dose was 1.1 g/kg. The average time to deliver the monthly HyQvia dose was approximately 2 hrs. HyQvia infusions were administered through 1 to 3 injection sites, and the majority of infusions (85.8%) were administered through 2 infusion sites using 12 mm to 14 mm needles.

Study Results

The analysis of the primary endpoint employing appropriate post-hoc strategies to handle intercurrent events and missing outcome values using multiple imputation revealed a relapse rate of

15.5% (95% CI: 8.36, 26.84) in the HyQvia and 31.7% (95% CI: 21.96, 43.39) in the placebo groups. The estimated treatment difference in the proportion of subjects who experienced a relapse was -16.2 (95% CI: -29.92, -1.27), favouring HyQvia over the placebo.

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

Primary and Secondary Immunodeficiency

In Study 160603, no consistent temporal association or increase in incidence or severity between adverse reactions and the presence of anti-rHuPH20 antibodies was observed.

The effect of exposure to antibodies capable of binding to Recombinant Human Hyaluronidase of HyQvia was evaluated for approximately 1000 days in Study 160603 and the open-label extension Study 160902, combined (see 14 CLINICAL TRIALS).

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

In Study 161403, anti-rHuPH20 binding antibodies with titers ≥1:160 were detected in 7/62 (11.3%) subjects in the HyQvia arm and 1/70 (1.4%) subject in the placebo arm. The presence of binding antibodies was not associated with an increased incidence of TEAEs based on limited data. No local or systemic reactions were attributed to the presence of anti-rHuPH20 antibodies. No subject developed neutralizing anti-rHuPH20 antibodies.

In the open-label extension Study 161505, 14/79 (17.7%) subjects had anti-rHuPH20 binding antibodies with titers ≥1:160. The presence of binding antibodies was not associated with an increased incidence of TEAEs based on limited data. One subject had transient positivity of neutralizing antibodies which was not associated with any TEAE or with loss of the rHuPH20 effect.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In single-dose toxicity studies with IG, 10% no adverse effects were observed at a dose of 5000 mg/kg in mice and 2000 mg/kg in rats. Repeat dose toxicity was not investigated for IG, 10% since a human protein in any xenogenic animal model would either be metabolized more quickly or cause severe antigenic reactions that are not representative for humans.

A chronic toxicity study was performed in mice to determine the potential toxicity of rHuPH20 as well as de novo produced anti-rHuPH20 antibodies. No adverse effects were observed, neither in the at a daily to weekly dose of 1 mg/kg (120,000 U/kg), which is 1600 times higher than the typical monthly human dose. Repeat-dose and chronic toxicity of rHuPH20 was evaluated in a 39-week repeated-dose toxicity study in cynomolgus monkeys. There were no adverse effects observed at a

weekly dose of up to 2 mg/kg (240,000 U/kg), which is 3200 times higher than the typical monthly human dose.

Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of IG, 10% or rHuPH20.

GenotoxicityAn in vitro mutagenicity test was performed for IG, 10% and there was no evidence of mutagenicity observed. Studies to evaluate the mutagenic potential of rHuPH20 have not been conducted.

Reproductive and Developmental Toxicology

No studies were conducted with IG, 10% since the metabolization of polyclonal human IG, 10% does not lead to any degradation of the product that could cause reproduction or developmental toxicity.

No adverse effects on fertility were observed in mice, rabbits and cynomolgus monkeys exposed to antibodies that bind to rHuPH20 and species-specific hyaluronidase.

Developmental studies in mice demonstrated that administration of rHuPH20 did not produce teratogenicity or signs of maternal toxicity at doses up to 18 mg/kg/day (2.2×10^6 U/kg/day), which is 28,800 times higher than the typical monthly human dose. Maternal doses of 9 and 18 mg/kg/day were associated with reduced fetal weight and an increased number of fetal resorptions. No adverse effects on fetal development were observed at a maternal dose of 3 mg/kg/day (360,000 U/kg/day), which is 4800 times higher than the typical monthly human dose.

In a peri-and post-natal reproduction trial, female mice were dosed daily with rHuPH20 from implantation through lactation and weaning. There were no adverse effects on gestation, parturition, lactation and maternal behavior or on the development of the male or female offspring of the treated female mice in terms of sexual maturation, learning and memory of offspring, or their ability to produce another generation of offspring at doses up to 9 mg/kg/day (1.1×10^6 U/kg/day) which is 14,400 times higher than the typical monthly human dose.

Studies were conducted in male and female rabbits to evaluate the potential effect of rHuPh20 and anti-rHuPH20 antibodies on fertility and embryo-fetal development with postnatal assessments. Male and female animals received six SC doses of rHuPH20 prior to mating and one booster dose two weeks after mating. There were no effect on mating and fertility at a repeated-dose of 0.76 mg/kg (90, 000 U/kg) which is 1200 times higher than the typical monthly human dose. Maternal anti-rHuPH20 antibodies transferred to their offspring during gestation had no effect on embryo-fetal or postnatal development or offspring mating and fertility.

Juvenile Toxicity

A juvenile toxicity study was performed in mice to determine the potential toxicity of rHuPH20 as well as de novo produced anti-rHuPH20 antibodies. No adverse effects were observed, at a daily to weekly dose of 1 mg/kg (120,000 U/kg), which is 1600 times higher than the typical monthly human dose.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

HyQvia

Normal Immunoglobulin (Human) 10% and Recombinant Human Hyaluronidase

Read this carefully before you start taking HyQvia and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about HyQvia.

Serious Warnings and Precautions

• Immunoglobulin (Human) products have been reported to be associated with heart and blood circulation problems such as heart attack, stroke and blood clots (thrombosis). Some of these risk factors include obesity, old age, prolonged periods of immobilization, high blood pressure, diabetes, or a history of heart disease. Thrombosis may also occur even in the absence of known risk factor.

Talk to your doctor if you have risk factors for these kinds of conditions.

• Do not use HyQvia at home until you get instructions and training from your healthcare professional. When using HyQvia at home, you must assign a guardian person who will help you watch out for allergic reactions, stop the infusion, and get help if necessary

What is HyQvia used for?

HyQvia is used to treat adults and children with primary immunodeficiency diseases (PI), and secondary immunodeficiency diseases (SI).

HyQvia is used in adult patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) after having their CIDP symptoms stabilized with previous intravenous immunoglobulin (IVIG) treatments. CIDP is characterised by chronic inflammation of the peripheral nerves that causes muscle weakness and/or numbness mainly in the legs and arms. It is believed that the body's own defense system attacks the peripheral nerves and causes nerve damage and inflammation. Immunoglobulins present in HyQvia are thought to help protect the nerves from being damaged by the immune system.

How does HyQvia work?

The recombinant human hyaluronidase is a protein that makes it easier for the immunoglobulins to be infused (dripped) under the skin and to reach your blood system.

The vial of immunoglobulins has been prepared from the blood of healthy people. Immunoglobulins are produced by the human body's immune system. They help your body to fight infections caused by bacteria and viruses or maintain the balance in your immune system (referred to as immunomodulation). The medicine works in the same way as the immunoglobulins naturally present in the blood.

What are the ingredients in HyQvia?

Medicinal ingredients: Human normal immunoglobulin, 10%

Non-medicinal ingredients: glycine, water for injection

Recombinant human hyaluronidase: calcium chloride dihydrate, edetate disodium dihydrate, human albumin, sodium chloride, sodium hydroxide, sodium phosphate dibasic dihydrate

HyQvia comes in the following dosage forms:

HyQvia contains two solutions for subcutaneous (SC) infusion under the skin. It is supplied as a package containing one vial of human normal immunoglobulin 10% and one vial of recombinant human hyaluronidase. HyQvia is available in 25, 50, 100, 200 and 300 mL vial sizes of immunoglobulin, each supplied with a corresponding vial of hyaluronidase.

Do not use HyQvia if:

- you are allergic to immunoglobulins, hyaluronidase, recombinant hyaluronidase or any of the other ingredients of this medicine (see What are the ingredients in HyQvia?).
- if you have antibodies against immunoglobulin A (IgA) in your blood. This may occur if you have IgA deficiency. Since HyQvia contains trace amounts of IgA, you might have an allergic reaction.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HyQvia. Talk about any health conditions or problems you may have, including if you:

- Have or had any kidney, liver, or heart problems or history of blood clots
- Have an IgA deficiency, have antibodies to IgA
- Have a history of severe allergic reactions to IgG antibodies or other blood products
- Are pregnant, trying to become pregnant or are breast feeding.
- Have high blood pressure

Other warnings you should know about:

- Do not infuse HyQvia into or around an infected or red swollen area on your skin because it may cause the infection to spread.
- You may experience side effects (for example dizziness or nausea) during treatment with HyQvia that might affect the ability to drive and use machines. If this happens, you should wait until the reactions have disappeared before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with HyQvia:

- Vaccinations: HyQvia may reduce the effect of some vaccines such as measles, rubella, mumps and chicken pox. Before you get any vaccines, tell your healthcare provider that you take HyQvia.
- Effects on blood tests: HyQvia contains many different antibodies, some of which can affect blood tests (serological tests). Tell your doctor about your treatment with HyQvia before any blood test.

How to take HyQvia:

- Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Also, see the "Detailed Instructions for Use" provided below.
- **HyQvia has to be infused under the skin (subcutaneous administration).** Do not infuse HyQvia into your veins (intravenously) nor into muscle (intramuscularly).
- Treatment with HyQvia will be started by your doctor or nurse, but you may be allowed to use the medicine at home once you have received the first few infusions under medical supervision and you (and/or your guardian) have been adequately trained.
- You should be trained on how to infuse the drug, how to use the pump or syringe driver, recording your treatment in your treatment diary, recognizing side effects and what to do about them.
- You and your doctor will decide if you can use HyQvia at home. Do not begin treatment with HyQvia at home until you have received complete instructions.
- You will take the hyaluronidase first. Make sure you infused the entire vial of hyaluronidase, even if you will not use up the entire vial of immunoglobulin. Then, within 10 minutes, you will take the immunoglobulin through an infusion pump. You must carefully follow your doctor's instructions regarding the dose, infusion speed and schedule for infusing HyQvia so that your treatment works for you.
- Your doctor may perform blood tests regularly to check your IgG level and adjust your dosage.

Usual dose:

Primary and Secondary Immunodeficiency

Your doctor will calculate the correct dose for you based on your body weight, any previous treatment you may have received and your response to treatment. In the beginning you will receive one quarter of this dose at 1 week intervals. This will be increased step-wise to larger doses at 3- to 4-week intervals with the next infusions. Sometimes your doctor may recommend that larger doses are split and given at two or three sites at once. Your doctor may also adjust your dose depending on your response to treatment.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Your doctor will calculate the correct dose for you based on your body weight, any previous treatment you may have received and your response to treatment. In the beginning you will receive one quarter of this dose at 1 week intervals. This will be increased step-wise to larger doses at 2- to 4-week intervals with the next infusions. Sometimes your doctor may recommend that larger doses are split and given at two or three sites at once. Your doctor may also adjust your dose depending on your response to treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much HyQvia contact your doctor as soon as possible.

Missed Dose:

Do not infuse a double dose of HyQvia to make up for a missed dose. If you think that you have missed a dose speak to your doctor as soon as possible.

What are possible side effects from using HyQvia?

These are not all the possible side effects you may have when taking HyQvia. If you experience any side effects not listed here, tell your healthcare professional.

After HyQvia infusion a temporary, soft swelling may occur around the infusion site, which may last 1 to 3 days, due to the volume of fluid infused.

The following local reactions may occur at the site of infusion and generally go away in a few hours: mild or moderate pain, redness, swelling, itching.

Local reactions are less likely after the first few infusions.

The most likely side effects of HyQvia, that occurred at rates of 5% or higher, are: headache, fatigue, nausea, fever, increase blood pressure, increased levels of enzymes made by your pancreas, abdominal pain, back pain, and pain in arms or legs.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Serious allergic reaction Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting, dizziness		√	√
Swelling in your brain Bad headache with nausea, vomiting, stiff neck, fever and sensitivity to light		√	√
Kidney problem Reduced urination, sudden weight gain or swelling in your legs		√	√
Blood clot Pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site		√	√
Liver or blood problem Brown or red urine, fast heart rate, yellow skin or eyes		√	√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Lung problem Chest pain or trouble breathing, blue lips or extremities		√	√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). You can take the product out of the refrigerator and store it at a temperature up to 25°C for 3 months. Do not use the product after the expiry date shown on the vial and carton even if the 3 month period is not over. Do not freeze. Do not shake.

Keep the vials in the outer carton in order to protect from light.

Do not use this medicine if the solutions are cloudy or have particles or deposits. After opening, dispose of any unused solutions in the vials.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

Detailed Instructions for Use are provided in the section below.

1. Remove HyQvia from the box:

- Allow vials to reach room temperature. This may take up to 60 minutes. Do not use heating devices including microwave.
- Do not heat up or shake HyQvia.
- *Check each vial of HyQvia before using*:
- **Expiration date:** Do not use beyond expiration date.
- **Colour:**
  - The recombinant human hyaluronidase should be clear and colourless.
  - The human normal immunoglobulin 10% can be clear and colourless to pale yellow.
  - If either liquid is cloudy or has particles, do not use.
  - Do not use the product if it does not have the cap.

2. Gather all supplies:

Dual vial unit(s) of HyQvia, infusion supplies (subcutaneous needle set, solution container (bag or syringe), sterile clear bandage and tape, pump tubing, transfer devices, syringes, gauze and tape), sharps container, pump, and treatment logbook and other supplies as needed.

Prepare the pump: program the infusion pump according to prescribed infusion rates and manufacturer's instructions

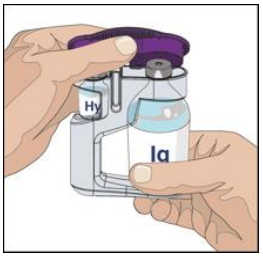
3. Prepare a clean work area.

4. Wash hands:

Wash your hands thoroughly. Place all gathered supplies and open them as directed by your healthcare professional.

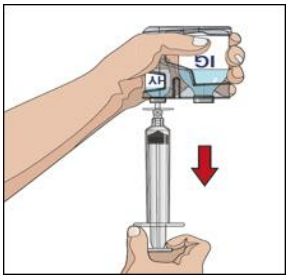
5. Open HyQvia dual vial unit(s):

- Remove purple protective caps to expose the vial stoppers.
- Prepare to transfer the recombinant human hyaluronidase component of HyQvia by wiping each vial stopper with an alcohol swab, if directed and allow to air dry (at least 30 seconds).



6. Prepare recombinant human hyaluronidase vial (HY):

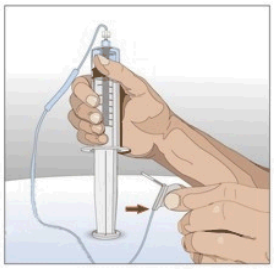
- Remove the smaller sterile syringe from package and attach to a non-vented spike or needle (device).
- Pull back on the plunger, fill the smaller syringe with air equal to the amount of in the recombinant human hyaluronidase, labeled with the letters 'HY'.
- Remove the cap of needle/non-vented transfer device.
- Insert the tip of the needle/non-vented transfer device into the center of the vial stopper and push straight downward. Push the air into the vial.
- Turn the vial upside down, with the needle/non-vented transfer device remaining in the vial. The syringe tip will be pointing upward.
- Withdraw the full contents of the recombinant human hyaluronidase into the syringe.
- Repeat above steps, if more than one vial of recombinant human hyaluronidase is needed for your dose.
- If possible, combine all of the recombinant human hyaluronidase needed for the entire dose of IgG into the same syringe.
- Point the syringe tip up and remove any air bubbles by pointing the syringe tip up and gently tapping the syringe with your finger. Slowly and carefully push the plunger to remove any remaining air.



7. Prepare the needle set with the recombinant human hyaluronidase (HY):

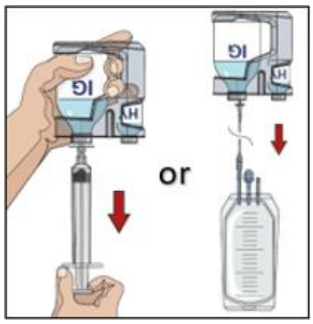
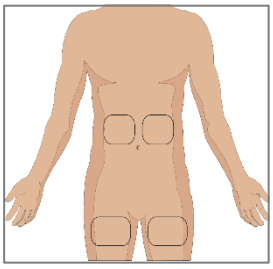
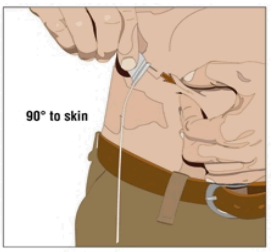
- Attach the syringe filled with recombinant human hyaluronidase to the needle set
- Push the plunger of smaller syringe to remove the air and fill the needle set up to the needle wings with the recombinant human hyaluronidase.

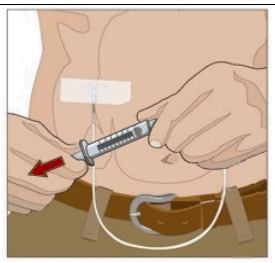
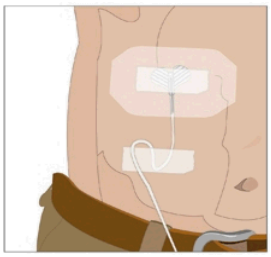
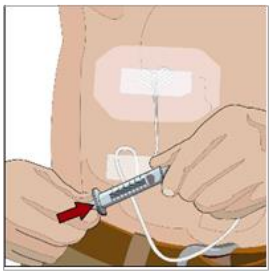
Note: Your healthcare professional may recommend using a "Y" connector (for more than one site) or other needle set configuration.



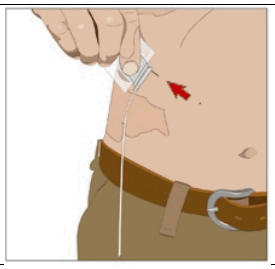
8. Prepare human normal immunoglobulin 10% vial (IG):

- Prepare to transfer the immunoglobulin 10% component of HyQvia vial(s), labeled with the letters 'IG', by wiping the vial(s) stopper with an alcohol swab, if directed and allow to air dry (at least 30 seconds).
- The human normal immunoglobulin 10% of HyQvia may be infused either
    - by pooling from the vials either into (a) larger

syringe or (b) an infusion bag as directed by your healthcare professional, depending upon the pump to be used; or • directly from the IG vial. Insert the spike of the vented pump tubing or spike and venting needle into human normal immunoglobulin 10% vial. Fill the administration pump tubing and set aside until the recombinant human hyaluronidase has been administered. • If more than one vial is required for a full dose, spike subsequent vials after the first vial has been fully administered.	a) b) 
9. Prepare the infusion site: • Choose an infusion site(s) in either the middle to upper abdomen at least 10 cm apart or thigh. See image for infusion site locations. • Select sites on the opposite sides of the body if instructed to infuse in two or three sites. • Do not infuse more than 600 mL in each site if you weigh 40 kg or more. • Do not infuse more than 300 mL in each site if you weigh less than 40 kg. • You may have to infuse smaller amounts if you cannot tolerate those infusion volumes. Talk to your doctor. • Avoid bony areas, visible blood vessels, scars and any areas of inflammation or infection. • Rotate infusion sites by choosing opposite sides of the body between future infusions. • As instructed by your health care professional, clean the infusion site(s) with an alcohol swab. Allow to dry (at least 30 seconds).	 
10. Insert the needle: • Remove the needle cover. Firmly grasp and pinch at least 2 to 2.5 cm of skin between two fingers. • Insert needle completely to the wings of the needle with a rapid motion straight into the skin at a 90-degree angle. Wings of needle should lay flat on the skin. • Secure needle in place with sterile tape. Repeat this step if you have a second infusion site.	

11. Check for proper needle placement before starting the infusion if instructed by your healthcare professional.	
12. Secure the needle to the skin: • Secure the needle(s) in place by putting a sterile clear bandage over the needle. • Check infusion site(s) occasionally throughout the infusion for dislodgement or leaking. • Ask your doctor about the needle size appropriate for you. Any change of needle size would have to be supervised by your doctor.	
13. Administer the recombinant human hyaluronidase infusion first: • Slowly push the plunger of the smaller syringe with the recombinant human hyaluronidase at an initial rate per infusion site to approximately 1 to 2 mL per minute and increase as tolerated. • If using a pump, prepare the pump to infuse the recombinant human hyaluronidase at an initial rate per infusion site of 60 to 120 mL/hour and increase as tolerated.	
14. Administer the human normal immunoglobulin 10%: • After infusing all of the content of the smaller syringe (recombinant human hyaluronidase), remove the syringe from the hub of the needle set. • Attach the pump tubing or, the larger syringe containing human normal immunoglobulin 10% to the needle set. Administer the human normal immunoglobulin 10% with a pump at the rates prescribed by your healthcare professional and start the infusion. It is very important to infuse the medicine at the correct speed.	
15. Flush the pump tubing when the infusion is complete if instructed by your healthcare professional: If instructed by your healthcare professional, attach a saline bag to the pump tubing/needle set to push the human normal immunoglobulin 10% up to the needle wings.	
• **Remove needle set:** • Remove the needle set by loosening the dressing on all edges. • Pull the needle wings straight up and out. • Gently press a small piece of gauze over the needle site and cover with a protective dressing. • Throw away the needle(s) into the sharps container.	

- Dispose of the sharps container using instructions provided with the container, or contact your healthcare professional.



- **Record the infusion:**
  - Remove the peel-off label from HyQvia vial, which has the product lot number and expiration date, and place the label in your treatment record/log book.
  - Write down the date, time, dose, site(s) of infusion (to assist in rotating sites) and any reactions after each infusion.
  - Throw away any unused product in the vial and the disposable supplies as recommended by your healthcare professional.
- Follow up with doctor as directed.

If you want more information about HyQvia:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (https://www.takeda.com/en-ca), or by calling 1-800-268-2772.

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