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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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

HyQvia is indicated as replacement therapy for primary humoral immunodeficiency (PI) and secondary humoral immunodeficiency (SI) in adult patients.

1.1 Pediatrics

Pediatrics (< 18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of HyQvia in pediatric patients has not been established. Therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS and 7.1.3 Pediatrics

1.2 Geriatrics

HyQvia was evaluated in 7 subjects over age 65 in the clinical trial. The available data are too limited to draw safety conclusions (see 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), or 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

- **For subcutaneous (SC) administration only.** Do not administer intravenously (IV) or intramuscularly.
- HyQvia should be administered by a healthcare professional, caregiver or self-administered by the patient after appropriate training.
- For self-administration, provide the patient with instructions and training for infusion, including the recognition of possible severe adverse reactions and measures to be taken in case these occur.
- 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.
- Individualize the IG, 10% dose based on the patient's pharmacokinetics and clinical response. HyQvia can be used to administer a full therapeutic dose in one to two sites every three or four weeks, after a gradual ramp-up dosing interval.
- Adjust the frequency and number of infusion sites taking into consideration volume, total infusion time, and tolerability so that the patient receives the same weekly equivalent IgG dose.

4.2 Recommended Dose and Dosage Adjustment

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. Adjust dosage and treatment interval as necessary based on serum IgG trough levels and infection rates.

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 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 interval based on

the weekly equivalents. The first infusion of HyQvia should be given one week after the last treatment with the previous immunoglobulin.

4.3 Administration

- 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.
- Visually inspect both components of HyQvia for discoloration and particulate matter prior to administration.
- Allow refrigerated product to come to room temperature before use. Do not use heating devices including microwaves.
- Do not shake.
- Do not mix the two components of HyQvia.
- See detailed instructions in PATIENT MEDICATION INFORMATION.

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 is infused at a rate of 1 to 2 mL/minute per infusion site or as tolerated.

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

The following initial infusion rates of IG, 10% are recommended per infusion site (see Table 1).

Table 1: 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 upper abdomen and thighs. Avoid bony prominences, or areas that are scarred, inflamed or infected.

If two sites are used, the two infusion sites should be on contra lateral sides of the body. Administer half the total volume of two components of HyQvia in each site.

4.4 Missed Dose

If a patient misses a dose, administer the missed dose as soon as possible and then resume scheduled treatments as applicable.

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 2: 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)	Units	
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 2**Error! Reference source not found.** (eg., 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 individu al 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

Thrombembolic 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

There is no information of the effects of HyQvia on the ability to drive or operate an automobile or other heavy 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.

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 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 antibodies to IgA potentially are at greater risk of developing potentially severe hypersensitivity and anaphylactic reactions.

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 no adequate data from the use of HyQvia in pregnant women. 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

There are no safety data on the use of HyQvia in breast-feeding women available.

Physicians should balance the potential risks and only prescribe HyQvia if clearly needed.

7.1.3 Pediatrics

HyQvia was evaluated in 36 unique patients between 2 and 17 years of age, 23 of which were less than 12 years of age. The safety in the long-term use of the rHuPH20 component of HyQvia is limited.

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 infuse at the minimum infusion rate practicable.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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.

8.2 Clinical Trial Adverse Reactions

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 7. Adverse reactions occurring in patients ≥ 18 years of age are listed in Table 3.

Table 3: 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
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.

Six subjects, 2 children and 4 adults, 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.

In the clinical trial, no temporal association between adverse reactions and the presence of antibodies capable of binding to the Recombinant Human Hyaluronidase of HyQvia could be demonstrated.

There was no increase in the incidence or severity of adverse reactions in subjects who developed antibodies to Recombinant Human Hyaluronidase of HyQvia. In all subjects, antibody titers decreased despite continued treatment.

The effect of exposure to antibodies capable of binding to Recombinant Human Hyaluronidase of HyQvia for periods longer than this clinical trial has not been evaluated.

The local adverse reactions are listed by frequency in Table 4. 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 4: 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.

Immunogenicity of Recombinant Human Hyaluronidase

Antibodies binding to rHuPH20: A total of 15 out of 120 subjects in three clinical trials who were treated with HyQvia developed a high titer (≥ 1:160) of antibody capable of binding to Recombinant Human Hyaluronidase. These antibodies were not capable of neutralizing Recombinant Human Hyaluronidase. There was no indication that development of binding antibody to Recombinant Human Hyaluronidase influences occurrence of adverse events.

8.3 Less Common Clinical Trial Adverse Reactions

General Disorders and Administration Site Conditions: Burning sensation, hyperhidrosis, infusion site discoloration, infusion site induration, feeling hot, infusion site paresthesia
Gastrointestinal Disorders: Abdominal distention
Investigations: Direct Coombs' test positive
Musculoskeletal and Connective Disorders: Musculoskeletal chest pain
Nervous System Disorders: Paresthesia
Skin and Subcutaneous Tissue Disorders: Pruritus, Urticaria
Renal and Urinary Disorders: Hemosiderinuria
Vascular disorders: Blood pressure increased

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

9.1 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.

9.2 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.3 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 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 immunoglobulin 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 immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

10.3 Pharmacokinetics

The pharmacokinetics of HyQvia was evaluated during the clinical study 160603 in patients with PID 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 5, as compared to data for intravenous administration of IG, 10% obtained in the same study.

Table 5: Pharmacokinetic Parameters of 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

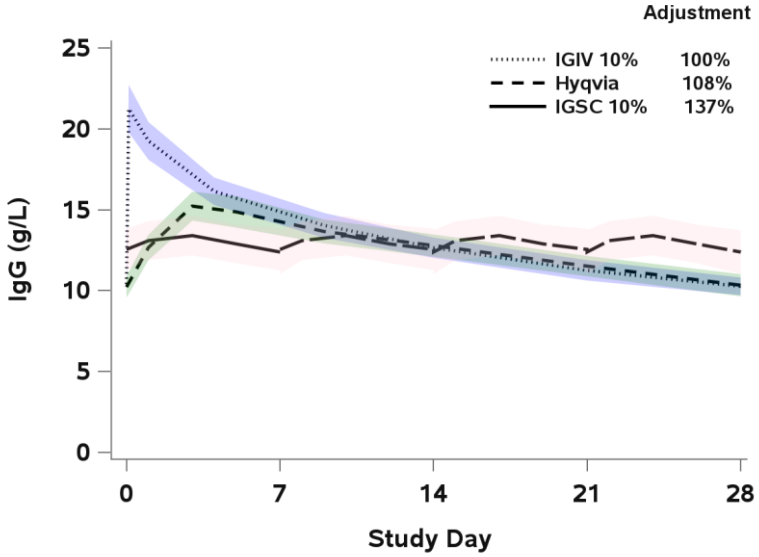
[b] Standardized to a 7 day interval

[c] N=58 HyQvia

[d] Apparent clearance

A mean concentration-time plot of subjects administered IGSC weekly (Study 160601), IGIV administered every 4 weeks (Study 160601 and Study 160603) and HyQvia administered every 4 weeks (Study 160603) in 129 subjects (12 years and older) is shown in Figure 1. The concentration-time profile of HyQvia is similar to that of intravenous (IGIV) administration but without the high peak. The peak to trough variation is more similar to subcutaneous (IGSC) administration.

Figure 1: Pharmacokinetic Comparison of Mean Ig G Values for HyQvia *vs*. Intravenously and Subcutaneously Administered Immunoglobulin Infusion 10% (Human)*



* IGIV and HYQVIA data at 28 day dosing interval; IGSC data at 7 day dosing interval; IGSC dotted line shows weekly dose extrapolated over 21 additional days.
Note: Bands show pointwise two-sided 95% confidence intervals for the mean at different time points

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator 2°C to 8°C (36°F to 46°F).

Do not return HyQvia to the refrigerator after it has been stored at room temperature. 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 6) 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 6: 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		Herpesviridae	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 Trial Design and Study Demographics

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

In the pivotal efficacy trial (Study 160603), 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.

Table 7: Summary of Clinical trials in Primary Immunodeficiency

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: IGI, 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 160603 (Efficacy trial)

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. 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.

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%).

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.

14.2 Study Results

Study 160603 (Efficacy trial)

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.

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 8. The secondary endpoints evaluated in the efficacy trial were the annual rate of all infections and other efficacy measures.

Table 8: 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 9.

Table 9: 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 6.33)	2.08 (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.

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 patients with primary immunodeficiency diseases (PI) and with secondary immunodeficiency diseases (SI).

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 contains immunoglobulin (IgG) antibodies, collected from human plasma donated by healthy people. The antibodies help your body to fight off bacterial and viral infections. The hyaluronidase part of HyQvia is a protein that makes it easier for the IgG antibodies to be infused under the skin and absorbed into your body.

How does HyQvia work?

Immunoglobulins are antibodies found in people's blood. Antibodies are part of the immune system (the body's natural defence system) and help your body to fight infections.

HyQvia is used in patients who do not have enough antibodies in their blood (PI patients) or have a weaken immune system (SI patients), and get frequent infections. Regular and sufficient doses of HyQvia can raise abnormally low immunoglobulin levels in your blood to normal levels (replacement therapy).

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

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 is supplied as a pack containing one vial of recombinant human hyaluronidase, and one vial of human normal immunoglobulin 10%. HyQvia is available in 25, 50, 100, 200 and 200 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?).

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 a IgA antibody deficiency or a history of severe allergic reactions to IgG antibodies or other blood products
- Are pregnant, trying to become pregnant or are breast feeding.

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.
- The effects of long-term use of recombinant human hyaluronidase on pregnancy, breast-feeding and male fertility are currently not known. Your body may form antibodies against recombinant human hyaluronidase, and this could affect your body's own hyaluronidase. However, these antibodies did not affect fertility and pregnancy in studies with animals.

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.

How to take HyQvia:

- Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
- HyQvia has to be infused under the skin (subcutaneous administration).
- 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 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. 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.

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% should be clear and colourless or pale yellow.
  - If either liquid is cloudy or has particles, do not use.

Cap: Protective cap is on the dual vial unit. Do not use the product if it does not have the cap.

2. Gather all supplies:

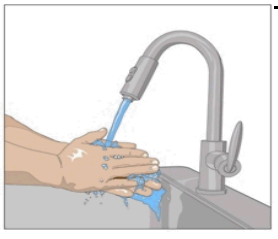
Items include: dual vial unit(s) of HyQvia, infusion supplies (subcutaneous needle set, solution container (bag or syringe), sterile clear bandage and tape, pump tubing, transfer devices, syringes, gauze and tape), sharps container, pump, and treatment logbook and other supplies as needed.

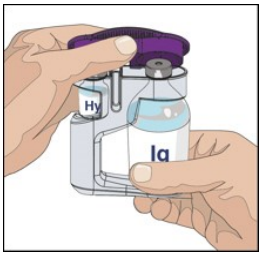
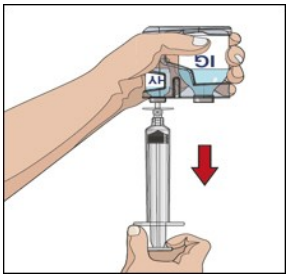
Prepare the pump: program the infusion pump according to prescribed infusion rates and manufacturer's instructions

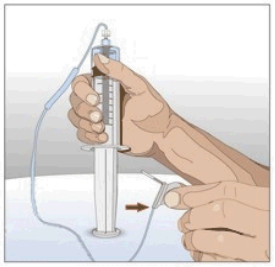
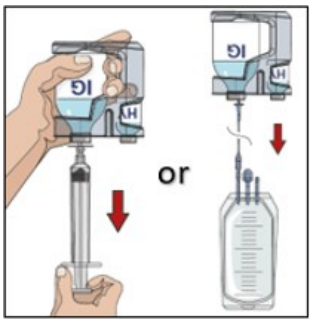
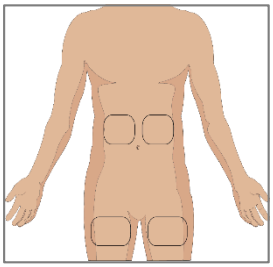
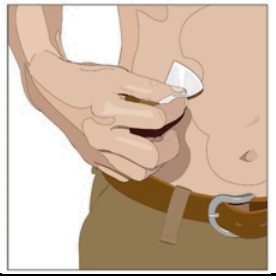
3. Prepare a clean work area.

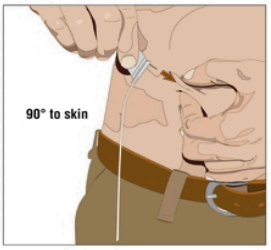
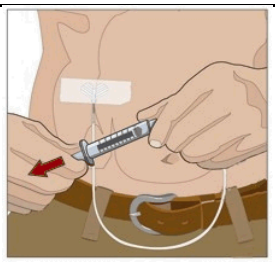
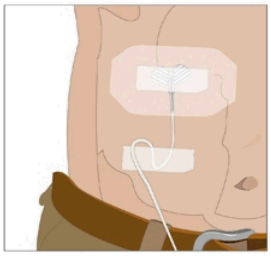
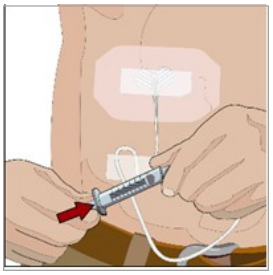
4. Wash hands:

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 recombinant human hyaluronidase in the HY vial(s). • 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 by wiping each vial 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 or thigh. See image for infusion site locations. o Select sites on the opposite sides of the body if instructed to infuse in two sites for doses above 600 mL. • 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).	 

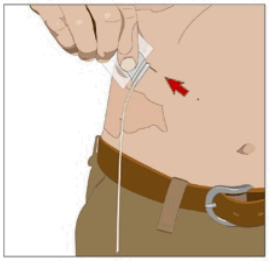
10. Insert the needle: • Remove the needle cover. Firmly grasp and pinch at least 2 to 2.5 cm of skin between two fingers. • Insert needle completely to the wings of the needle with a rapid motion straight into the skin at a 90-degree angle. Wings of needle should lay flat on the skin. • Secure needle 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.

16. 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.



17. 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 physician as directed.

Usual dose:

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. The recommended starting dose is one that supplies 400 to 800 mg of active substance per kg of bodyweight per month. 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 sites at once. Your doctor may also adjust your dose depending on your response to treatment.

Overdose:

If you think you 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 common side effects of HyQvia are: Headache, Fatigue, Nausea, and Fever.

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		√	√
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). 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.

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 1-800-268-2272.

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