▼ This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

HYQVIA® (Normal Immunoglobulin (Human) with vorhyaluronidase alfa) solution for infusion

1 NAME OF THE MEDICINE

Normal Immunoglobulin Infusion 10% (Human) with vorhyaluronidase alfa.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

HYQVIA is a dual vial unit consisting of one vial of Normal Immunoglobulin 10% (Human) and one vial of vorhyaluronidase alfa. Vorhyaluronidase alfa enables the facilitated subcutaneous administration of Normal Immunoglobulin (Human).

Normal Immunoglobulin
HYQVIA vials contain 2.5g in 25mL, 5.0g in 50mL, 10.0g in 100mL, 20.0g in 200mL or 30.0g in 300mL of the active Normal Immunoglobulin (Human) [Immunoglobulin G (IgG) 100 mg/mL].

The active ingredient in HYQVIA is a human plasma-derived immunoglobulin, concentration of 100 mg/mL (10% w/v), produced from large pools of human plasma by a modified Cohn-Oncley cold ethanol fractionation, yielding an intermediate immunoglobulin G, referred to as Precipitate G. During the cold ethanol plasma fractionation manufacturing process, the level of viral burden in a plasma pool has been largely reduced, as demonstrated by viral spiking experiments. Precipitate G is further purified by means of a weak cation-exchange and anion-exchange chromatography.

To reduce further a possible viral transmission to a minimal level, a triple step of viral inactivation (TVR inactivation), [solvent detergent (S/D), nano-filtration (35nm), and incubation at a low pH and elevated temperature (30ºC to 32ºC, pasteurisation for 21 to 23 days)] was incorporated into the downstream purification. Thus, the active ingredient normal immunoglobulin has been subjected to a rigorous elimination for both lipid and non-lipid enveloped viruses.

The manufacturing processes do not affect the composition of the immunoglobulin from the normal human plasma origin. The distribution of the immunoglobulin G (IgG) sub-classes formulated in this product comprises $IgG_1 \geq 56.9\%$, $IgG_2 \geq 26.6\ \%$, $IgG_3 \geq 3.4\%$, and $IgG_4 \geq 1.7\%$.

It contains immunoglobulin A (IgA) at a trace level, which is not more than 0.14 mg/mL. The preparation is a sterile, non-pyrogenic, isotonic solution with Osmolality of 240 to 300 mOsmol/kg and a pH of 4.6 to 5.1. At this low pH the formation of the IgG aggregates is much reduced, leading to reduction in the incidence of infusion-related adverse reactions. It contains glycine which acts as a stabilising agent for the proteins. The product does not contain preservatives. The composition of normal immunoglobulin is shown in Section 6.1 LIST OF EXCIPIENTS.

Vorhyaluronidase alfa
HYQVIA vials contain 200 units in 1.25mL, 400 units in 2.5mL, 800 units in 5mL, 1600 units in 10mL or 2400 units in 15mL of the active vorhyaluronidase alfa [160 U/mL].

The vorhyaluronidase alfa of HYQVIA is used as a permeation enhancer. It is produced from genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase rHuPH20. The purified hyaluronidase glycoprotein contains 447 amino acids with an approximate molecular weight of 61,000 Daltons. This component is supplied as a sterile, clear, colourless, ready-for-use solution and has an approximate pH of 7.4 and an osmolality of 290 to 350 mOsm. Each vial contains 160 U/mL of vorhyaluronidase alfa 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. It does not contain preservatives.

Due to comprehensive virus testing at the Master Cell Bank, Working Cell Bank and bulk harvest stage, effective virus reduction during the purification process and the use of pharmaceutical grade human albumin as an excipient with no other materials of human or animal origin involved in the manufacturing process, vorhyaluronidase alfa provides for high margins of safety with respect to viruses. The composition of vorhyaluronidase alfa is shown in Section 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

Solution for infusion for subcutaneous use.

Appearance
HYQVIA is a dual vial unit consisting of one vial of Normal Immunoglobulin 10% (Human) and one vial of vorhyaluronidase alfa. Normal Immunoglobulin is a clear or slightly opalescent and colourless or pale-yellow solution. Vorhyaluronidase alfa is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

HYQVIA is indicated in adults and children 2 years of age and older for:

- Replacement therapy in:
  - Primary Immunodeficiency Disease (PID) and
  - Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

- Immunomodulatory therapy in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as maintenance therapy after stabilisation with intravenous immunoglobulin (IVIG).

4.2 DOSE AND METHOD OF ADMINISTRATION

HYQVIA must only be administered SUBCUTANEOUSLY. The dose and dose regimens are dependent on the indication.

Treatment should be commenced and initially monitored under the supervision of a physician experienced in the treatment of immunodeficiency/CIDP. HYQVIA is for single use in one patient only.

Dosage
HYQVIA must be administered sequentially beginning with the vorhyaluronidase alfa followed by Normal Immunoglobulin.

The dose level may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimen is given as a guideline.

1. **Replacement therapy**

The recommended dose of Normal Immunoglobulin of HYQVIA for patients is 0.3 to 0.6 g/kg body weight infused at 3- to 4-week intervals.

The first infusion of HYQVIA should be given one week after the last treatment with the previous immunoglobulin. At the initiation of treatment, it is recommended that the treatment intervals for the first infusions be gradually prolonged from a 1-week dose to a 3- or 4-week dose.
The cumulative monthly dose of IG 10% should be divided into 1-week, 2-week etc. doses according to the planned treatment intervals with HYQVIA.

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

Week	Infusion Number	Dose Interval	Example for 30 grams per 4 weeks
1	1st infusion	1-week-dose	7.5 grams
2	2nd infusion	2-week-dose	15 grams
3	No infusion		
4	3rd infusion	3-week-dose	22.5 grams
5	No infusion		
6	No infusion		
7	4th infusion (if required)	4-week-dose	30 grams

Patients previously treated with immunoglobulin administered intravenously
For patients switching directly from IVIG, or who have a previous intravenous dose of immunoglobulin that can be referenced, the medicinal product should be administered at the same dose and at the same frequency as their previous intravenous immunoglobulin treatment. 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 naive to immunoglobulin treatment
For patients, naive to immunoglobulin treatment, or those currently being administered immunoglobulin subcutaneously (SC), the initial dose of HYQVIA is 0.3 to 0.6 g/kg.

Patients previously treated with immunoglobulin administered subcutaneously
For patients directly switching from an immunoglobulin treatment administered subcutaneously, the first infusion of HYQVIA should be given one week after the last treatment with the previous immunoglobulin.

The dosage regimen should achieve the desired clinical response and a sustained level of IgG. Trough levels should be measured in order to adjust the dose and dosage interval.

Paediatric population
The dosing schedule for children and adolescents is the same as for adults. The dosing is based on body weight and adjusted to the clinical outcome.

2. Immunomodulatory therapy in CIDP

Before initiating therapy, the weekly equivalent dose should be calculated by dividing the planned dose by the planned dose interval in weeks. The typical dosing interval range for HYQVIA is 3 - to 4-weeks. The recommended subcutaneous dose is 0.3 to 2.4 g/kg body weight per month, administered in 1- or 2-sessions over 1- or 2-days.

The patient`s clinical response should be the primary consideration in dose adjustment. The dose may need to be adapted to achieve the desired clinical response. In clinical deterioration, the dose may be increased to the recommended maximum of 2.4 g/kg monthly. If the patient is clinically stable, periodic dose reductions may be needed to observe whether the patient still needs IG therapy.

A titration schedule that permits gradual dose increase over time (ramp-up) is recommended to ensure the patient's tolerability until the full dose is reached. During the titration schedule, the calculated HYQVIA dose and recommended dose intervals must be followed for the first and second infusions. Depending on the treating physician's discretion, in patients who tolerate the first 2 infusions well, subsequent infusions may be administered by gradually increasing doses and dose intervals, considering the volume and total infusion time. An accelerated titration schedule may be considered if the patient tolerates the SC infusion volumes and the first 2 infusions. Doses less than or equal to 0.4 g/kg may be administered without a titration schedule, provided acceptable patient tolerance.

The following dose regimens are given as a guideline:
Patients must be on stable doses* of IVIG. Before initiating therapy with the medicinal product, the weekly equivalent dose should be calculated by dividing the last IVIG dose by the IVIG dose interval in weeks. The starting dose and dosing frequency are the same as the patient's previous IVIG treatment. The typical dosing interval for HYQVIA is 4-weeks. For patients with less frequent IVIG dosing (greater than 4-weeks), the dosing interval can be converted to 4-weeks while maintaining the same monthly equivalent IgG dose.

As shown in Table 2 below, the calculated one-week dose (1st infusion) should be administered 2 -weeks after the last IVIG infusion. One week after the first dose, the next weekly equivalent dose (2nd infusion) should be administered. A titration schedule can take up to 9 -weeks (Table 2), depending on the dosing interval and tolerability.

*(*Variations in the dosing interval of up to ±7 days or monthly equivalent dose amount of up to ±20% between the subject's IgG infusions are considered a stable dose.*)

Table 2: Initial Treatment Interval/Dosage Ramp-Up Schedule

Week*	Infusion number	Dose interval	Example for 100 g every 4-weeks
1	No infusion		
2	1st infusion	1-week-dose	25 g
3	2nd infusion	1-week-dose	25 g
4	3rd infusion	2-week-dose	50 g
5	No infusion		

6	4th infusion	3-week-dose	75 g
7	No infusion		
8	No infusion		
9	5th infusion	4-week-dose	100 g (Full dose reached)

** 1st infusion starts 2-weeks after the last IVIG dose.*

Paediatric population
The dosing schedule for children and adolescents is the same as for adults. The dosing is based on the calculated weekly equivalent dose and adjusted to the clinical outcome.

Method of administration
HYQVIA must only be administered **SUBCUTANEOUSLY**. Do not infuse intravenously. For each full or partial vial of Normal Immunoglobulin used, the full contents of vorhyaluronidase alfa should be administered.

HYQVIA is comprised of two vials. Each vial of Normal Immunoglobulin 10% (Human) is supplied with the appropriate corresponding quantity of vorhyaluronidase alfa as stated in Table 3. The full contents of the vorhyaluronidase alfa vial should be administered regardless of whether the full content of the Normal Immunoglobulin 10% (Human) vial is administered.

For the ease of identification, the vorhyaluronidase alfa vial is labelled HY and the Normal Immunoglobulin 10% (Human) vial is labelled IG**.**

Table 3: HYQVIA administration scheme

Vorhyaluronidase alfa (160 U/mL)	**Normal Immunoglobulin 10% (Human)**	
Volume (mL)	**Protein (g)**	**Volume (mL)**
1.25	2.5	25
2.5	5	50
5	10	100
10	20	200
15	30	300

The two components of HYQVIA must be administered sequentially through the same needle beginning with the vorhyaluronidase alfa followed by Normal Immunoglobulin 10% (Human), as described below.

Infusion site leakage can occur during or after subcutaneous administration of immunoglobulin, including HYQVIA. Consider using longer needles and/or more than one infusion site.

The HYQVIA components may be infused using a variable rate, electromechanical pump. The pump must have the ability to titrate the flow rate up or down if required to improve tolerability. To ensure maximum flow rates, use a subcutaneous needle set that is 24 gauge and labelled for high flow rates.

The suggested site(s) for the infusion 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 infusion sites, the sites should be at least 10 cm apart. Avoid bony prominences and areas that are scarred, inflamed or infected.

Volume per site

Replacement therapy

Administer up to 600 mL per site for patients whose body weight is greater than or equal to 40 kg and up to 300 mL per site for patients whose body weight is less than 40 kg.

A second site can be used at the discretion of the physician and patient based on tolerability and total volume. If a second site is used, administer half the total volume of rHuPH20 of HYQVIA in each site.

Immunomodulatory therapy in CIDP

On a given infusion day, the maximum infusion volume should not exceed 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg. If the maximum daily dose limit is exceeded or the patient cannot tolerate the infusion volume, the dose may be administered over multiple days in divided doses with 48 to 72 hours between doses to allow absorption of infusion fluid at the infusion site(s). The dose can be administered at 1, 2, or 3 infusion sites with a maximum infusion volume of 600 mL per site (or as tolerated). If using three sites, the maximum is 400 mL per site.

Infusion rate

First, the full dose of vorhyaluronidase alfa solution is infused at a rate of 1 to 2 mL/minute per infusion site or as tolerated. Within 10 minutes of completing the infusion of vorhyaluronidase alfa, the infusion of the required dose of Normal Immunoglobulin has to be initiated at the same needle site.

The rate of administration of the Normal Immunoglobulin of HYQVIA should be ramped-up, at least for the first several infusions. If the patient tolerates these infusions at the full dose and maximum rate, adjust both the time intervals and number of rate changes of the ramp-up used for successive infusions at the discretion of the physician and patient. If two infusion sites are used, the total dosages of the vorhyaluronidase alfa and Normal Immunoglobulin each have to be divided before start of the infusion.

The following infusion rates of the Normal Immunoglobulin are recommended:

- Patients with a body weight of 40 kg or above: Normal Immunoglobulin should be infused at an initial rate of 10 mL/hour/infusion 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/site for the initial one or two infusions. For subsequent infusions, the rate can be adjusted to a maximum of 300 mL/hour/site.
- Patients with a body weight under 40 kg: Normal Immunoglobulin should be infused at an initial rate of 5 mL/hour/infusion 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/site for the initial one or two infusions. For subsequent infusions, the rate can be adjusted to a maximum of 160 mL/hour/site.

Home treatment

If self-administration at home or other appropriate setting is planned, the healthcare professional should provide the patient or the carer with adequate training in terms of the correct technique of subcutaneous administration and the correct recognition and management in cases of acute adverse reactions.

For detailed instructions, please see **INSTRUCTIONS FOR ADMINISTRATION**.

4.3 CONTRAINDICATIONS

HYQVIA is contraindicated in:

- patients who have had a history of anaphylactic or severe systemic reactions to the administration of IgG,
- IgA deficient patients with antibodies to IgA and a history of hypersensitivity,
- patients with known systemic hypersensitivity to hyaluronidase or vorhyaluronidase alfa or known systemic hypersensitivity to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

HYQVIA must not be administered intravenously.

If HYQVIA is inadvertently administered into a blood vessel, patients could develop shock. In the case of shock, current medical standards for shock treatment should be observed.

It is strongly recommended that every time HYQVIA is administered to a patient, the name and batch number of the product is recorded in order to maintain a link between the patient and the batch number of the product.

Hypersensitivity
Severe hypersensitivity reactions may occur, even in patients who have tolerated previous treatment with human normal immunoglobulin. In case of hypersensitivity, discontinue the HYQVIA infusion immediately and institute appropriate treatment.

The Normal Immunoglobulin contains trace amounts 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.

Rarely, human normal immunoglobulin can induce an anaphylactic reaction with a fall in blood pressure, even in patients who had tolerated previous treatment with human normal immunoglobulin. If a patient is at high risk for any hypersensitivity/anaphylaxis reactions, the product should be administered only where supportive care is available for life threatening reactions.

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin, by initially injecting the product slowly
- are carefully monitored for any symptoms throughout the infusion period. Certain adverse reactions may occur more frequently in patients naive to human normal immunoglobulin, patients switched from an alternate product or when there has been a long interval since the previous infusion. Such patients should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after the administration.

Patients on self-home treatment and/or their guardian should also be trained to detect early signs of hypersensitivity reactions.

Spread of localised infections
HYQVIA should not be injected at or around an infected or acutely inflamed area because of the danger of spreading a localised infection.

No chronic changes in the skin were observed in the clinical studies. Patients should be reminded to report any chronic inflammation, nodules or inflammation that occurs at the infusion site and lasts more than a few days.

Thromboembolism
Thromboembolic events may occur following treatment with immunoglobulin products, including HYQVIA. These include myocardial infarction, cerebral vascular accident, deep vein thrombosis and pulmonary embolism.

Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders and prolonged periods of immobilisation, obesity, diabetes mellitus, acquired or inherited thrombophilic disorder, a history of vascular disease and a history of a previous thrombotic or thromboembolic event.

For patients at risk of thrombosis, HYQVIA should be administered at the minimum dose and infusion rate practicable. Patients should be adequately hydrated before administration and these individuals should be monitored for signs and symptoms of thrombosis.

Reactions reported to occur with intravenously administered immunoglobulins
The following reactions have been reported to occur with IVIG treatment and may occur with subcutaneous immunoglobulin (SCIG) treatment. Thromboembolic events (myocardial infarction, cerebral vascular accident, deep vein thrombosis, and pulmonary embolism), renal dysfunction/failure, aseptic meningitis syndrome, haemolysis, Transfusion Related Acute Lung Injury (TRALI) have been observed with Immunoglobulin Infusion (Human), 10% administered intravenously and cannot be excluded with use of HYQVIA.

Aseptic meningitis syndrome
Aseptic meningitis syndrome (AMS) has been reported to occur in association with human immunoglobulin treatment. Discontinuation of human immunoglobulin treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following human immunoglobulin treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high-dose (2 g/kg) intravenous immunoglobulin treatment.

AMS may occur more frequently in female patients.

Haemolysis
Immunoglobulin products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coomb's test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to immunoglobulin therapy due to enhanced red blood cells (RBC) sequestration. Immunoglobulin product recipients should be monitored for clinical signs and symptoms of haemolysis.

Use in renal impairment
Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death may occur in patients receiving IVIG therapy, especially those containing sucrose. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, sepsis, hyperviscosity, paraproteinemia, concomitant nephrotoxic medicinal products or age over 65.

Periodic monitoring of renal function and urine output is particularly important in patients judged 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. In case of renal impairment or if renal function deteriorates, HYQVIA discontinuation should be considered.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the registered IVIG products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of immunoglobulin products that do not contain these excipients may be considered. HYQVIA does not contain sucrose, maltose or glucose.

In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and consider infusing HYQVIA at lower, more frequent doses.

Pathogen safety
HYQVIA is manufactured using components of human blood, which may contain the causative agents of hepatitis and other viral diseases, and theoretically Creutzfeldt-Jacob Disease (CJD) agents. Prescribed manufacturing procedures utilised at the plasma collection centres and plasma-testing laboratories are designed to reduce the risk of transmitting viral infection.

Important elements of the rigorous screening include: careful selection of donors for plasma pools, viral testing at multiple stages, and the application of a rigorously validated method of testing. Prior to the manufacturing of the bulk drug substance, the plasma pool is tested for viral markers using HIQ-PCR method (Hyland Immuno Quality Assured Polymerase Chain Reaction is nucleic acid amplification test, NAT), which allows for the detection of viruses at a level of 500 genome equivalents (ge) per mL of the plasma.

The inclusion of Solvent Detergent (S/D) into the manufacturing process, which is effective for removal of enveloped-lipid viruses (HIV-1, HBV and HCV) and nano-filtration and incubation at elevated temperatures and low pH, which are effective for both enveloped and non-enveloped-lipid viruses (HAV and Parvovirus B19), would theoretically provide an assurance that the viral infectious agents have been removed. In addition, Normal Immunoglobulin of HYQVIA contains specific antibodies directed against parvovirus B19. Despite the use of those rigorous tests and triple viral inactivation (TVR), as discussed in the Section 2 DESCRIPTION, a possibility of transmitting infectious agent cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

Appropriate vaccinations (hepatitis A and B) should be considered for immune competent patients who receive regular/repeated treatment with HYQVIA.

Immunogenicity of vorhyaluronidase alfa
Eighteen percent (15 of 83) of subjects receiving HYQVIA in the pivotal PID clinical studies developed non- neutralising antibodies to the vorhyaluronidase alfa component. The potential exists for such antibodies to cross-react with endogenous hyaluronidase, which is known to be expressed in the adult male testes, epididymis, and sperm. It is unknown whether these antibodies may interfere with fertilisation in humans. The clinical significance of these antibodies is not known.

14.4 percent (15 of 104) of subjects who received HYQVIA developed anti-rHuPH20 binding antibodies at least once in CIDP studies that included 257 patient-years of follow-up. Two subjects developed anti- rHuPH20 neutralising antibodies. No efficacy or safety issues were identified with binding or neutralising antibody positivity.

One (1/44; 2.3%) 4-year-old female subject in the paediatric PID study developed positive anti-rHuPH20 binding antibodies at Epoch 2 Month 6 which persisted at all time points up to and including study completion/termination at Epoch 2 Month 36. The antibodies were non-neutralising, and no correlation of adverse reactions (no increase in incidence or severity) with the presence of binding antibodies to rHuPH20 was observed. The clinical significance of persistent positive anti-rHuPH20 binding antibodies in paediatric patients is uncertain.

Hypersensitivity to vorhyaluronidase alfa
Any suspicion of allergic or anaphylactic like reactions following vorhyaluronidase alfa administration requires immediate discontinuation of the infusion and standard medical treatment should be administered, if necessary.

Paediatric use
HYQVIA was evaluated in 44 paediatric patients with PID (aged 3 to 16 years old). Results of the study indicated similar safety profile to adults. HYQVIA has not been evaluated in clinical studies in paediatric or adolescent patients (0-18 years) with CIDP.

Use in the elderly
Replacement therapy
HYQVIA was evaluated in 7 subjects over age 65 in the clinical trial, and sufficient data is not available to determine whether safety of this product is different in this population.

Immunomodulatory therapy in CIDP
HYQVIA was evaluated in 13 subjects over the age of 65 in the pivotal clinical trial. No clinically significant differences in safety were observed between those 13 elderly subjects and the subjects 18 to 65 years of age.

Effect on laboratory tests
Interference with serological testing
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, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Infusions of immune globulin 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

Admixtures of HYQVIA with other drugs and intravenous solutions have not been evaluated. It is recommended that HYQVIA be administered separately from other drugs or medications that the patient may be receiving. The product should not be mixed with immunoglobulin products from other manufacturers.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Clinical experience with immunoglobulins suggests that no harmful effects of Normal Immunoglobulin on fertility are to be expected. With HYQVIA, currently data is not available for clinical safety on development of the reproductive system.

Reversible infertility has been observed in male and female guinea pigs immunized to produce antibodies to hyaluronidase. However, antibodies to hyaluronidase did not influence reproduction following immunization of mice, rabbits, sheep, or cynomolgus monkeys. The effects of antibodies that bind to vorhyaluronidase alfa on human fertility are unknown.

Use in pregnancy
There are no adequate data from the use of HYQVIA in pregnant women. Maternally administered immunoglobulins have been shown to cross the placenta, increasingly during the third trimester.

The effects of antibodies to the vorhyaluronidase alpha component of HYQVIA on the human embryo or on human foetal development are unknown.

Developmental studies in mice demonstrated that administration of hyaluronidase did not produce teratogenicity or signs of maternal toxicity at doses up to 18 mg/kg (2.2 x 106 U/kg), which is 28,100 times higher than the typical monthly human dose. Maternal doses of 9 and 18 mg/kg were associated with reduced foetal weight and an increased number of foetal resorptions. No adverse effects on foetal development were observed at a maternal dose of 3 mg/kg (360,000 U/kg), which is 4700 times higher than the typical monthly human dose.

Nine women treated with HYQVIA were enrolled in a prospective, uncontrolled, open-label, multicentre post-authorisation Pregnancy Registry. Seven mothers continued HYQVIA, and two mothers were treated with immune globulin other than HYQVIA during the pregnancy. Of the 8 pregnancies with known outcomes, there were 8 live births. There were no specified labour or

delivery complications. Two out of 5 infants whose mothers took HYQVIA during pregnancy had congenital abnormalities (cleft lip without cleft palate and talipes calcaneovalgus). Data from the HYQVIA Pregnancy Registry are insufficient to establish causality. The registry findings are limited due to the small sample size, potential selection bias favouring retrospective enrolment of mothers of infants with congenital abnormalities, absence of foetal outcomes in some exposed maternal-foetal pairs, and incomplete data on other possible causes.

Healthcare providers should carefully consider the potential risks and benefits for each specific patient before prescribing HYQVIA. HYQVIA should be given to a pregnant woman only if clearly indicated.

Use in lactation
There are no adequate data from the use of HYQVIA in lactating women. In animal studies, maternal antibodies binding to vorhyaluronidase alfa were transferred to offspring during lactation. In a peri-and post-natal reproduction trial, female mice were dosed daily with recombinant human hyaluronidase from implantation through lactation and weaning. There were no adverse effects on gestation, parturition, lactation and maternal behaviour 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 (1.1 x106 Unit/kg) which is 14,200 times higher than the typical monthly human dose.

The effects of antibodies that bind to vorhyaluronidase alfa of HYQVIA transferred during human lactation are unknown. Healthcare providers should carefully consider the potential risks and benefits for each specific patient before prescribing HYQVIA.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

HYQVIA has no or negligible influence on the ability to drive and use machines. Patients who experience adverse reactions (such as dizziness and nausea) during treatment should wait for these to resolve before driving or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile
The most frequently reported adverse reactions (ARs) of HYQVIA occurring in clinical studies for replacement therapy in PID at a rate of 0.203 per infusion were local reactions. Among the 365 intravenous infusions, systemic ARs occurred at a rate of 0.42 per infusion. Of the 1,129 HYQVIA infusions, systemic ARs occurred at a rate of 0.20 per infusion.

The most frequently reported systemic ARs were headache, fatigue and pyrexia. The majority of these ARs were mild to moderate.

The most common adverse reactions observed in >5% of study subjects in clinical studies of HYQVIA for CIDP were local reactions, headache, pyrexia, nausea, vomiting, diarrhoea, fatigue (including asthenia and malaise), erythema, pruritus, abdominal pain, oedema (including oedema peripheral, peripheral swelling, localised oedema and skin oedema), arthralgia, back pain, and pain in extremity.

Normal immunoglobulin (human)
Patients naive to immunoglobulin may experience a higher frequency of adverse effects including those of a minor nature.

Cases of transient aseptic meningitis, transient haemolytic reactions, increase in serum creatinine level and/or acute renal failure have been observed with human normal immunoglobulin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis have been rarely observed with intravenous and subcutaneous administration of immunoglobulin products.

The following additional adverse reactions have been reported for subcutaneously administered immunoglobulin products in general, listed by MedDRA System Organ Class and Preferred Term in order of severity:

- Immune system disorders: Hypersensitivity reaction
- Nervous system disorders: Paraesthesia, Tremor
- Cardiac disorders: Tachycardia
- Vascular disorders: Flushing, Pallor, Peripheral coldness
- Respiratory, thoracic, and mediastinal disorders: Dyspnoea
- Gastrointestinal disorders: Paraesthesia oral
- Skin and subcutaneous tissue disorders: Swelling face, Urticaria, Dermatitis allergic, Hyperhidrosis, Pruritus
- Musculoskeletal and connective tissue disorders: Back pain, Musculoskeletal stiffness
- General disorders and administration site conditions: Chest discomfort, Feeling hot
- Investigations: Alanine aminotransferase increased

Vorhyaluronidase alfa
The most frequent adverse reactions reported during post-marketing use of vorhyaluronidase alfa in similar formulations administered subcutaneously for the dispersion and absorption of subcutaneously administered fluids or medicinal products have been mild local injection site reactions such as erythaema and pain. Oedema has been reported most frequently in association with large volume subcutaneous fluid administration.

Tabulated list of adverse reactions

Replacement therapy in PID
The safety of HYQVIA was evaluated in a 12-month clinical study in patients with PID. The analysis of safety was conducted on 83 subjects in the intent-to-treat population who received at least one treatment of HYQVIA. A total of 1359 infusions of HYQVIA were administered during the study, 1129 infusions in 81 subjects during the 12-month safety and efficacy period.

Local reactions, reported in 50.6% of subjects and at a rate of 0.203 per infusion, were the most frequently reported ADRs during the efficacy period. The most frequently reported systemic ADRs were headache, fatigue, and pyrexia. The majority of these ADRs were mild to moderate and did not necessitate discontinuing the infusions.

Table 4: Clinical Trial Adverse Reactions				
System Organ Class (SOC)	**Preferred MedDRA Term**	**Rate of Reaction per Infusion[b] (N=1129)**	**Frequency per Subject**	**Percent of subjects (N=81)**
Metabolism and nutrition disorders	Decreased appetite	0.003	Common	2.5%
Nervous system disorders	Headache	0.032	Very Common	18.5%
	Migraine	0.006	Common	3.7%
	Dizziness	0.003	Common	3.7%
	Burning sensation	0.002	Common	1.2%
Vascular disorders	Hypertension[c]	0.005	Common	3.7%
	Blood pressure decreased	0.001	Common	1.2%
Respiratory, thoracic, and mediastinal disorders	Nasal congestion	0.003	Common	1.2%
Gastrointestinal disorders	Vomiting	0.007	Common	4.9%
	Nausea	0.004	Common	3.7%
	Abdominal pain upper	0.003	Common	2.5%
	Diarrhoea	0.001	Common	1.2%
	Oral pain	0.001	Common	1.2%
Skin and subcutaneous tissue disorders	Erythema	0.001	Common	1.2%
	Rash maculo-papular	0.001	Common	1.2%
Musculoskeletal and connective tissue disorders	Myalgia	0.009	Common	3.7%
	Arthralgia	0.003	Common	2.5%
	Groin Pain	0.002	Common	2.5%
	Pain in extremity	0.002	Common	1.2%
	Musculoskeletal chest pain	0.001	Common	1.2%
Reproductive system and breast disorders	Vulvovaginal pruritus	0.001	Common	1.2%
	Oedema genital	0.001	Common	1.2%
General disorders and administration site conditions	Local reactions (Total)	0.203	Very Common	50.6%
	• Discomfort/pain	0.108	Very Common	43.2%
	• Erythema	0.028	Common	17.3%
	• Swelling/Oedema	0.024	Common	17.3%
	• Pruritus	0.017	Common	9.9%
	• Infusion site mass	0.003	Common	3.7
	• Nodule	0.002	Common	2.5%
	• Infusion site warmth	0.002	Common	2.5%
	• Infusion site hematoma	0.001	Common	1.2%
	• Infusion site haemorrhage	0.001	Common	1.2%
	Fatigue	0.012	Common	9.9%
	Pyrexia	0.009	Common	6.2%
	Oedema peripheral	0.002	Common	2.5%
	Chills	0.002	Common	1.2%
	Malaise	0.002	Common	1.2%
	Asthenia	0.001	Common	1.2%
	Feeling abnormal	0.001	Common	1.2%
	Gravitational oedema	0.001	Common	1.2%

Investigations	Antibody test positive[d]	0.001	Common	1.2%
	Coombs test positive	0.001	Common	1.2%
	Lymphocyte count decreased	0.001	Common	1.2%
	White blood cell count decreased	0.001	Common	1.2%
	Weight decreased	0.002	Common	2.5%

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

[a] Excluding Infections

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

[c]Includes increased blood pressure

[d]A total of 13 subjects developed an antibody capable of binding to vorhyaluronidase alfa at least once during the study. In all but this one instance it was deemed unrelated by the investigator. These antibodies were not capable of neutralising vorhyaluronidase alfa.

Table 5: Adverse Drug Reactions (Excluding Infections) Occurring in >5% of Subjects (Study 160603: Safety Analysis Set)

	IVIG		**HYQVIA (Excluding Ramp-Up)**	
MedDRA Preferred Term	**Percent of Subjects with ADRs[a] N = 87**	**Rate of ADRs/Infusion[b] N = 365**	**Percent of Subjects with ADRs[a] N = 81**	**Rate of ADRs/Infusion[b] N = 1129**
INFUSION SITE PAIN	1.1%	0.003	32.1%	0.080
HEADACHE	25.3%	0.104	18.5%	0.032
INFUSION SITE ERYTHEMA	0.0%	0.000	12.3%	0.025
INFUSION SITE DISCOMFORT	0.0%	0.000	9.9%	0.027
FATIGUE	6.9%	0.022	9.9%	0.012
INFUSION SITE PRURITUS	0.0%	0.000	7.4%	0.015
PYREXIA	5.7%	0.016	6.2%	0.009
INFUSION SITE SWELLING	0.0%	0.000	6.2%	0.009
LOCAL SWELLING	0.0%	0.000	6.2%	0.005
NAUSEA	9.2%	0.022	3.7%	0.004
CHILLS	8.0%	0.025	1.2%	0.002

[a]ADR was defined as an adverse event (excluding infections) which is related to immunoglobulin infusion and/or vorhyaluronidase alfa as assessed by the investigator.

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

Paediatric study

HYQVIA was evaluated in a pivotal efficacy and safety study of paediatric patients, with a total of 44 subjects (aged 3 to 16 years of age). The study indicated similar safety profiles to adults. HYQVIA has not been evaluated in clinical studies in paediatric or adolescent patients (0-18 years) with CIDP.

Description of selected adverse reactions

Local reactions observed during the pivotal clinical study include mild swelling of the site (present in most infusions) due to the large volumes infused, but in general were not considered an adverse reaction unless they caused discomfort. Only two instances of local adverse reactions were severe, infusion site pain and infusion site swelling. There were two instances of transient genital oedema, one considered severe, that resulted from diffusion of HYQVIA from the infusion site in the abdomen. No skin changes were observed that did not resolve during the clinical study.

Immunomodulatory therapy in CIDP
The safety of HYQVIA was evaluated in two clinical studies (ADVANCE-1 and ADVANCE-3 Extension) in 104 unique patients with CIDP receiving 4085 infusions (Table 6). The overall observation period was 194 patient-years.

The following convention is used for the classification of the frequency of per subject adverse drug reaction (ADR) and is based on the Council for International Organisations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 6: Adverse Drug Reactions in HYQVIA CIDP ADVANCE-1 and ADVANCE-3 Extension studies

System Organ Class	Preferred MedDRA Term	Number and Rate (%) by Subject[‡] (N = 104)[†]	Category	Rate by (%) Infusions[§] (N = 4085)	Category
NERVOUS SYSTEM DISORDERS	Headache	29 (27.9%)	Very Common	3.84%	Common
	Dizziness	5 (4.8%)	Common	0.22%	Uncommon
	Paraesthesia	4 (3.8%)	Common	0.15%	Uncommon
	Tremor	4 (3.8%)	Common	0.12%	Uncommon
	Cerebrovascular accident and Ischaemic stroke	2 (1.9%)	Common	0.05%	Rare
	Migraine	1 (1.0%)	Uncommon	0.02%	Rare
CARDIAC DISORDERS	Tachycardia (including Sinus tachycardia)	4 (3.8%)	Common	0.17%	Uncommon
VASCULAR DISORDERS	Hypertension	12 (11.5%)	Very Common	0.44%	Uncommon
	Hypotension	3 (2.9%)	Common	0.07%	Rare
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS	Dyspnoea	3 (2.9%)	Common	0.07%	Rare
GASTROINTESTINAL DISORDERS	Nausea	17 (16.3%)	Very Common	0.64%	Uncommon
	Abdominal pain (including Abdominal pain lower and abdominal pain upper)	12 (11.5%)	Very Common	0.56%	Uncommon
	Diarrhoea	12 (11.5%)	Very Common	0.34%	Uncommon
	Vomiting	9 (8.7%)	Common	0.29%	Uncommon
	Abdominal distension	3 (2.9%)	Common	0.12%	Uncommon
SKIN & SUBCUTANEOUS TISSUE DISORDERS	Pruritus	9 (8.7%)	Common	0.49%	Uncommon
	Erythema	7 (6.7%)	Common	1.18%	Common
	Rash (including Rash erythematous and Rash macular)	5 (4.8%)	Common	0.34%	Uncommon
	Urticaria	1 (1.0%)	Uncommon	0.02%	Rare
	Arthralgia	13 (12.5%)	Very Common	0.69%	Uncommon

MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	Pain in extremity (including Limb discomfort)	10 (9.6%)	Common	0.76%	Uncommon
	Back pain	9 (8.7%)	Common	0.38%	Uncommon
	Myalgia	5 (5.0%)	Common	0.29%	Uncommon
	Musculoskeletal chest pain	3 (2.9%)	Common	0.17%	Uncommon
	Groin pain	1 (1.0%)	Common	0.02%	Rare
	Joint stiffness	1 (1.0%)	Uncommon	0.29%	Uncommon
GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS	Local reactions (Total)	41 (39.4%)	Very Common	16.06%	Very Common
	Infusion site erythema (including Injection site erythema)	23 (22.1%)	Very Common	9.84%	Common
	Infusion site pain (including Infusion site discomfort, Injection site pain and Puncture site pain)	17 (16.3%)	Very Common	1.35%	Common
	Infusion site pruritus (including Injection site pruritus and Puncture site pruritus)	14 (13.5%)	Very Common	0.81%	Uncommon
	Infusion site swelling (including Infusion site induration, Infusion site oedema, Injection site swelling, Injection site induration, and Injection site oedema)	14 (13.5%)	Very Common	2.64%	Common
	Infusion site bruising (including Infusion site haematoma, Infusion site haemorrhage, and Injection site haematoma)	5 (4.8%)	Common	0.17%	Uncommon
	Infusion site rash (including Injection site rash)	4 (3.8%)	Common	0.27%	Uncommon
	Infusion site reaction	4 (3.8%)	Common	0.12%	Uncommon

	(including Injection site reaction and Puncture site reaction)				
	Infusion site inflammation	3 (2.9%)	Common	0.07%	Rare
	Infusion related reaction	2 (1.9%)	Common	0.39%	Uncommon
	Infusion site induration (including Injection site induration)	2 (1.9%)	Common	0.15%	Uncommon
	Injection site paraesthesia	2 (1.9%)	Common	0.12%	Uncommon
	Infusion site mass (including Infusion site nodule)	1 (1.0%)	Uncommon	0.12%	Uncommon
	Asthenia, Fatigue, and Malaise	23 (22.1%)	Very Common	0.88%	Common
	Pyrexia	23 (22.1%)	Very Common	1.88%	Common
	Localised Oedema (including Peripheral swelling, Peripheral oedema, and Skin oedema)	6 (5.8%)	Common	0.17%	Uncommon
	Chills	4 (3.8%)	Common	0.12%	Uncommon
	Burning sensation	2 (1.9%)	Common	0.17%	Uncommon
	Feeling hot	1 (1.0%)	Uncommon	0.07%	Rare

† N = number of subjects who were dosed at least once.
‡ Rate by subject = total number of subjects experiencing the ADR divided by total number of subjects multiplied by 100.
§ Rate by infusions = total number of adverse events (related and unrelated) divided by total number of infusions multiplied by 100.

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

IMMUNE SYSTEM DISORDERS: Hypersensitivity

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Influenza-like illness, infusion site leaking

The following adverse reactions have been identified and reported during post marketing use of vorhyaluronidase alfa administered subcutaneously for the dispersion and absorption of subcutaneously administered fluids or drugs.

The most frequently reported adverse experiences include injection site reactions such as

erythema and pain. Oedema has been frequently reported in conjunction with subcutaneous fluid administration.

Class Reactions
The following adverse reactions have been reported in subcutaneously administered immunoglobulin products.

IMMUNE SYSTEM DISORDERS: Anaphylactic shock, anaphylactic/anaphylactoid reactions, hypersensitivity reaction

NERVOUS SYSTEM DISORDERS: Paraesthesia, tremor

CARDIAC DISORDERS: Tachycardia

VASCULAR DISORDERS: Hypotension, flushing, pallor, peripheral coldness

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Dyspnoea

GASTROINTESTINAL DISORDERS: Paraesthesia oral

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Swelling face, urticaria, dermatitis allergic, hyperhidrosis, pruritus, exfoliative dermatitis

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Back pain, musculoskeletal stiffness

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Chest discomfort, feeling hot, injection site reaction (including urticaria, induration, warmth, haemorrhage, hematoma, and rash), infusion site leaking.

INVESTIGATIONS: Alanine aminotransferase increased.

INFECTIONS AND INFESTATIONS: Meningitis aseptic.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Consequences of an overdose of HYQVIA are unknown.

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Normal Immunoglobulin
IgG antibodies are protein molecules that are capable of specific interaction with molecules that are part of the membranes of infectious agents, foreign or abnormal cells, or toxic materials (antigens). Antibodies are produced by B lymphocytes, often with the help of T lymphocytes, macrophages, or dendritic cells. Following an initial interaction, some of the B-cells differentiate to memory cells, which upon encountering with the same infectious agent later in life, are capable of rapidly reproducing and producing increased quantities of the IgG antibodies specific to the same infectious agent.

The IgG molecules have two distinct and separable functions. One function is to bind specifically to the epitope in the antigen through the Fab end of the molecule, which is formed by the combination of the heavy and light chains. The other end of the IgG molecule, the Fc portion, can activate complement, bind to receptors on phagocytic cells to promote engulfment of the antigen/antibody complexes, and binding to the neonatal receptor which modulates the catabolism of IgG. In addition, binding of the Fc portion of the IgG molecule to regulatory receptors on B cells, T cells, and macrophages can modulate the activity of those cells, which may be useful in the control of autoimmune disease.

Thus, the mode of action of normal immunoglobulin mimics the action of the normal plasma immunoglobulin in a healthy adult individual having a broad spectrum of antibodies against infectious agents.

Vorhyaluronidase alfa

Hyaluronan is a polysaccharide found in the extracellular matrix of the connective tissue. It is depolymerised by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the extracellular matrix, hyaluronan has a very fast turnover with a half-life of approximately 0.5 days. The vorhyaluronidase alfa of HYQVIA increases permeability of the subcutaneous tissue by temporarily depolymerising hyaluronan. In the doses administered, vorhyaluronidase alfa of HYQVIA acts locally. The effects of the hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

Clinical trials

Replacement therapy in PID
A prospective, open-label, non-controlled, multi-centre trial was conducted 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 subcutaneously each week at 137% of the intravenous dose for approximately one year before transitioning to the HYQVIA trial. The remaining subjects were also 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

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, 3 weeks later the 4-week dose was administered. 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%). Median age was 35.0 years (range 4 to 78 years). Forty-four of the subjects were naive to subcutaneous treatment. Median serum IgG trough levels for the 6 months before enrolment were 1,033.5 mg/dL (range: 405 to 3,200 mg/dL) in subcutaneous-experienced subjects and 1,000 mg/dL (range: 636 to 3,200) in the subcutaneous-naïve subjects.

The 83 subjects received a total of 1359 infusions of HYQVIA during the entire trial. Of these, 1,129 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 IVIG 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 episodes of pneumonia treated as outpatients with oral antibiotics, during the 12-month efficacy period and one additional pneumonia that required hospitalisation during the ramp-up. Based on this, the annualised 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 7. The secondary endpoints evaluated in the efficacy trial were the annual rate of all infections and other efficacy measures.

Table 7: Summary of Infections and Other Secondary Efficacy Endpoints

Parameter	Annual Rate	
	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. Summary of infusions of intravenous administration compared to HYQVIA administration is presented in Table 8.

Table 8: Summary of Infusions

Parameter	IVIG	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%) of subjects attained the same 3- or 4-week dosing as their previous IVIG 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.

In a separate study evaluating subcutaneous treatment with Normal Immunoglobulin (Human) 10% a median of 21.43 sites were required each month with a median monthly infusion time of 5.35 hours.

Paediatric study

A prospective, open-label, non-controlled, multicentre trial was conducted in the United States of America to determine the efficacy, safety, immunogenicity, and pharmacokinetics (PK) of HYQVIA in paediatric subjects with PID who had received IVIG or SCIG treatment before enrolment into the trial. A total of 44 subjects were enrolled and dosed, and the median age of paediatric subjects was 9.5 years (range: 3 to 15 years). Of the enrolled subjects, 26 subjects (59.1%) were male, 18 subjects (40.9%) were female, and 40 subjects (90.9%) were White. Most subjects were not Hispanic or Latino (39 subjects [88.6%]).

Paediatric subjects switched to HYQVIA SCIG treatment schedule administered at doses (volumes and treatment intervals) typical for IVIG administration. Treatment intervals and doses gradually increased in a ramp-up phase to an interval of 3 or 4 weeks. The median exposure period to HYQVIA was 14.9 months. Overall, the median number of infusions per month was 1.1 (range: 1.0 to 1.5) and was comparable across the age groups. The median number of infusion sites per month was 2.2 (range: 1.1 to 2.9), with a similar median number for all age categories. There were no clinically meaningful differences in trough IgG levels across age groups.

The primary analysis for efficacy was based on the rate of acute bacterial infections (ASBIs), defined as bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess, per subject per year. Secondary analyses included the

annual rate of other infections and health resource utilisation outcome measures (e.g., days out of work/school/daycare).

The mean ASBI rate per year was 0.04 (with an upper 1-sided 99% confidence interval of 0.20, $p<0.001$), which met the predefined success rate of less than one ASBI per subject per year. One subject experienced two ASBIs of bacterial pneumonia, and there were no other episodes of serious bacterial infections reported in this trial. The mean rate of all infections per subject-year was 3.12, with an upper limit of the 95% CI of 3.95. The overall rate of infections per subject is consistent with results obtained in the pivotal clinical study. Paediatric subjects missed a mean (95% CI) of 5.0 (2.2 to 7.9) days of work/school/daycare.

Immunomodulatory therapy in CIDP

ADVANCE-1 Study

In a multicentre, randomised, 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 IVIG treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg body weight administered intravenously for at least 12 weeks before screening. Subjects did not undergo IVIG dependency testing prior to randomisation. 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.

The mean duration of exposure was 5.3 months in the HYQVIA group and 4.7 months in the placebo group. 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 were administered through 2 infusion sites only (85.8%) using 12 mm to 14 mm needles.

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 treatment difference was -16.2 (95% CI: -29.92, -1.27), favouring HYQVIA over placebo.

ADVANCE-3 Extension

Study 161505 was a Phase 3b, long-term, multicentre extension study to evaluate the long-term safety, tolerability, and immunogenicity of HYQVIA as maintenance therapy in adult subjects with CIDP who had received prior HYQVIA therapy (or placebo) in Study 161403. A total of 85 subjects who completed Study 161403 Epoch 1 without CIDP worsening and met the selection criteria for Study 161505 were enrolled and treated. The mean (SD) duration of exposure to HYQVIA was 31.1 (18.00) months (ranging from 0 to 77.3 months. The total exposure time was 219.9 patient-years. The safety outcomes were consistent with the known safety profile of HYQVIA and did not reveal any new safety concerns.

5.2 PHARMACOKINETIC PROPERTIES

Replacement therapy in PID
The pharmacokinetics (PK) of HYQVIA was evaluated during a clinical trial of adults with primary immunodeficiency disease (PID) after they achieved steady state at their 3- or 4-week dosing interval and underwent individual dose adjustment (see Section 5.1 PHARMACODYNAMIC PROPERTIES/CLINICAL TRIALS). For adults, 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 during HYQVIA treatment.

The AUC of HYQVIA compared to conventional SCIG administration was 20% higher. The absolute bioavailability of HYQVIA was 93.3% relative to intravenous immunoglobulin (IVIG).

The pharmacokinetic parameters of HYQVIA compared to intravenously administered Normal Immunoglobulin 10% are shown in Table 9. The mean IgG dose in weekly equivalents was 147 mg/kg ± 50 (range 134 to 160 mg/kg). The serum IgG trough levels are comparable: mean serum IgG trough with HYQVIA was 1,077 mg/dL compared to 1,095 mg/dL with intravenously administered Normal Immunoglobulin 10%. C max was lower with HYQVIA (1,607 mg/dL) than with intravenously administered Normal Immunoglobulin 10% (2,248 mg/dL). Time to reach maximum concentration of IgG following HYQVIA administration was 5 (3.3-5.1) days.

In the extension trial, reducing the dosing interval from 4 to 2 weeks resulted in a mean increase of 13% in serum immunoglobulin trough levels.

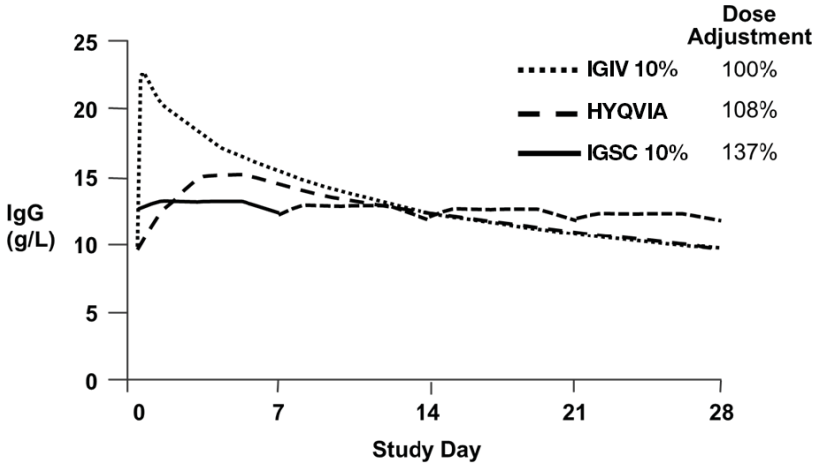
Table 9: Pharmacokinetic Parameters of HYQVIA Compared to Intravenously Administered Normal Immunoglobulin 10% (Human) (IVIG 10%)

	HYQVIA	IVIG
Number of Subjects	60	68
IgG Weekly Dose [mg/kg/week] Mean (SD) 95% CI	 147 (50) 134 to 160	 139 (55) 126 to 153
C max [mg/dL] Mean (SD) 95% CI	 1,607 (382) 1,508 to 1,706	 2,248 (547) 2,116 to 2,380
IgG Trough Levels [mg/dL][a] Mean (SD) 95% CI	 1,077 (275) 1,004 to 1,149	 1,095 (321) 1,017 to 1,174
AUC/week [g*days/L][b] Mean (SD) 95% CI	 91.4 (21) 85.9 to 96.8	 98.7 (24.3) 92.8 to 104.5
Bioavailability[c] Point estimate 90% CI	 93.3 91.4 to 95.2	 100% (defined) N/A
Clearance [mL/kg/day] Mean (SD) 95% CI	 1.6 (0.5)[d] 1.5 to 1.8	 1.4 (0.4) 1.3 to 1.5
Terminal Half-life [days] Mean (SD) 95% CI	 59.3 (36.1) 50 to 68.6	 41.6 (26.9) 35.1 to 48.1
T max [days] Median 95% CI	 5.0 3.3 to 5.1	 0.1 0.1 to 0.1

[a] N=58 for HYQVIA and N=67 for IVIG
[b] Standardised to a 7 day interval
[c] N=58 for HYQVIA
[d] Appearant clearance

Figure 2 shows mean concentration-time plot of IgG in subjects 12 years and older. The concentration-time profile of HYQVIA is similar to that of intravenous administration but without the high peak. The peak to trough variation is more similar to subcutaneous administration.

Figure 2
Pharmacokinetic Comparison of Mean IgG Values for HYQVIA vs. Intravenously and Subcutaneously Administered Normal Immunoglobulin 10% (Human)*



* IVIG and HYQVIA data at 28-day dosing interval; SCIG data at 7-day dosing interval; SCIG dotted line shows weekly dose extrapolated over 21 additional days.

Immunomodulatory therapy in CIDP
The pharmacokinetic profile of HYQVIA was not evaluated in the ADVANCE-1 study in patients with CIDP aged 18 years and older. Serum trough levels of total IgG were assessed throughout the study. Overall, during the treatment period with HYQVIA, serum trough levels of total IgG remained stable. For subjects who developed a relapse and switched to IVIG (n=6), the mean serum trough levels of total IgG also appeared stable throughout the treatment period with HYQVIA.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Genotoxicity studies were not performed as the hyaluronidase is the recombinant form of a naturally occurring protein; as such it is not expected to interact with DNA or other chromosomal material, nor has it been shown to transform cells and promote the growth of normal or malignant cells.

Carcinogenicity
Carcinogenicity studies were not performed as the hyaluronidase is the recombinant form of a naturally occurring protein; as such it is not expected to interact with DNA or other chromosomal material, nor has it been shown to transform cells and promote the growth of normal or malignant cells.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Composition of Normal Immunoglobulin (Human) [Immunoglobulin G (IgG) 100 mg/mL]
Active ingredient: Normal immunoglobulin (Human) contains at least 98% IgG
Stabilising agent: Glycine
Water for injection

Composition of vorhyaluronidase alfa strength (160 U/mL)
Active ingredient: vorhyaluronidase alfa
Excipients: dibasic sodium phosphate dihydrate, sodium hydroxide, human albumin 25%, calcium chloride, sodium chloride, disodium edetate, water for injection.

6.2 INCOMPATIBILITIES

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

For interactions, please refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

36 months from date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C – 8°C) for 36 months. Do not freeze.
Keep the vials in the outer carton in order to protect from light.
Do not use beyond the expiration date printed on the vial or carton.

Special precautions for handling
The product should be brought to room temperature before use.

Normal Immunoglobulin is a clear or slightly opalescent and colourless or pale-yellow solution. Vorhyaluronidase alfa is a clear, colourless solution. Visually inspect both components of HYQVIA for discolouration and particulate matter prior to administration. Allow refrigerated product to come to room temperature before use. Do not heat or microwave.

Do not shake.

Do not mix the components of HYQVIA prior to administration.

Do not use vented vial access devices to remove vorhyaluronidase alfa from vials.

Use aseptic technique when preparing and administering HYQVIA. In cases where more

than one vial of Normal Immunoglobulin or vorhyaluronidase alfa is required to obtain the required dose of the infusion, the Normal Immunoglobulin and/or vorhyaluronidase alfa should be prepared separately in appropriate solution containers before administration.

6.5 NATURE AND CONTENTS OF CONTAINER

Normal Immunoglobulin 10% (Human) vial
25, 50, 100, 200 or 300 mL of solution in a vial (Type I glass) with a stopper (bromobutyl rubber).

Vorhyaluronidase alfa vial
1.25, 2.5, 5, 10 or 15 mL of solution in a vial (Type I glass) with a stopper (chlorobutyl rubber).

Pack size

One vial of Normal Immunoglobulin 10% (Human) and one vial of vorhyaluronidase alfa in a dual vial unit.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

HYQVIA contains no antimicrobial preservative. Partially used vials should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS numbers
Normal Immunoglobulin 10% (Human): Not available
Vorhyaluronidase alfa: 757971-58-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd.
Level 39
225 George Street
Sydney, NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

27 April 2016

10 DATE OF REVISION

26 September 2025

Summary table of changes

Section Changed	Summary of new information
ALL	Minor editorial changes throughout; tables re-numbered.
4.1, 4.2, 4.4, 4.8, 5.1, & 5.2	Sections updated to include information related to treatment of PID in paediatric patients, and CIDP in adults and children. Instructions for Administration re-formatted.

INSTRUCTIONS FOR ADMINISTRATION

Do not use HYQVIA at home until you get instructions and training from your healthcare professional.

Your healthcare professional will decide which administration system is right for you. You will take vorhyaluronidase alfa first. Then, within 10 minutes, you will take the Normal Immunoglobulin through an infusion pump.

For the ease of identification, the vorhyaluronidase alfa vial is labelled HY and the Normal Immunoglobulin 10% (Human) vial is labelled IG.

Prepare HYQVIA vial(s):

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<tr><td>

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 or shake HyQvia.**
- *Check each vial of HYQVIA before using:*
  - **Expiration date:** Do not use beyond expiration date.
  - **Colour:**
    - The contents of vorhyaluronidase alfa (HY) should be clear and colourless.
    - The contents of Normal Immunoglobulin (IG) 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.

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2. Gather supplies:

Collect *all items* for your infusion. 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 and infusion pump (program pump per physician recommendation following manufacturer's instructions), and treatment logbook and other supplies as needed.

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3. Prepare a clean work area.

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4. Wash hands.

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

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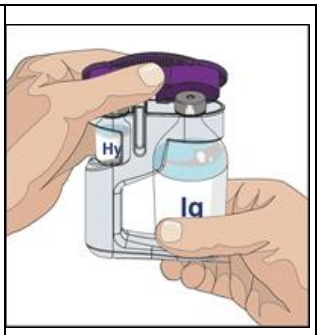
</table>

5. Open HyQvia dual vial unit:

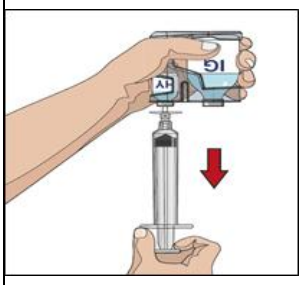
a. Remove the purple protective cap (s) and make sure the blue vial caps are removed. If not, manually remove the blue caps to expose the vial stoppers.

b. Wipe each stopper with a sterile alcohol wipe and allow to dry (at least 30 seconds).



6. Prepare the vorhyaluronidase alfa of HYQVIA (Labelled as "HY"):

- Remove the smaller sterile syringe from package and attach it to the needle/needle-less transfer device
- Pull back on plunger of the syringe to fill the smaller syringe with air equal to the amount in the HY vial.
- Remove the cap of needle/non-vented transfer device.
- Insert the tip of the needle/non-vented transfer device into the centre 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 HY vial(s) into the syringe.



Repeat the above steps, if more than one HY vial is needed for your dose. If possible, combine all the vorhyaluronidase alfa needed for the entire dose of IgG into the same syringe.

Point 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 vorhyaluronidase alfa (HY):

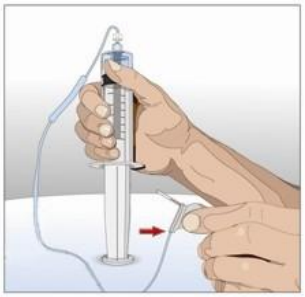
a. <u>If using the push method to deliver (HY):</u>

- Attach the syringe containing the vorhyaluronidase alfa (HY) to the subcutaneous needle set.
- Push the plunger of smaller syringe to remove the air and fill the needle set up to the needle wings with the vorhyaluronidase alfa.

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

b. <u>If using the pump method to deliver (HY):</u>

- Attach the syringe filled with vorhyaluronidase alfa (HY) to the pump tubing and attach the needle set
- Push the plunger of syringe (size may vary due to a larger volume) to remove the air and fill the pump tubing and needle set up to the needle wings with the vorhyaluronidase alfa.



8. Prepare the Normal Immunoglobulin of HYQVIA (Labelled as "IG"):

- Wipe each stopper with a sterile alcohol wipe and allow to dry (at least 30 seconds).Transfer the vial(s) labelled IG into either syringe(s), infusion bag or directly from the vial as shown by your healthcare professional:

a. If using syringe(s):

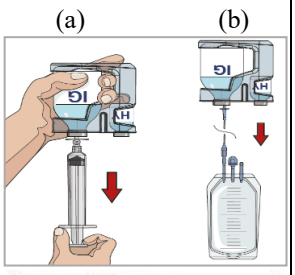
1. Attach a sterile syringe to a vented spike.
2. Insert the vented spike into the centre of the IG vial.
3. Turn the vial upside down and pull back on the plunger to pull the IG into the syringe(s).
4. Repeat these steps, if using multiple vials to achieve the desired dose.

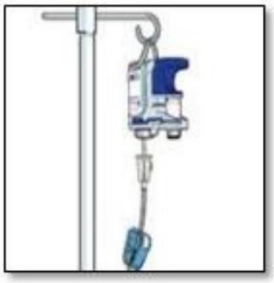
b. If using an infusion bag:

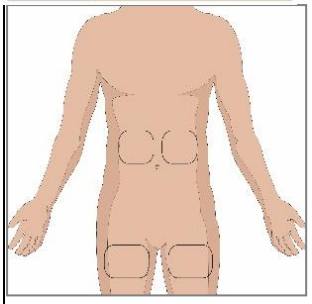
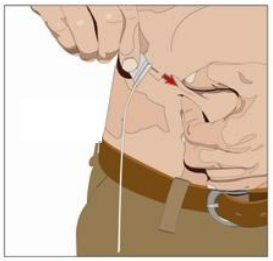
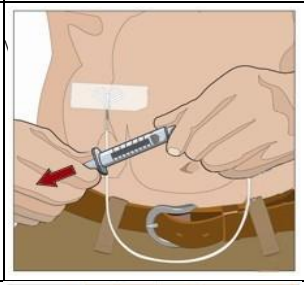
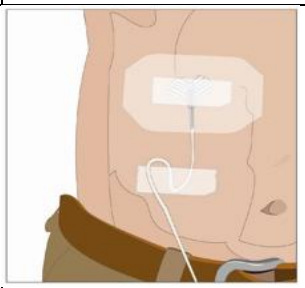
1. Insert the vented spike into the centre of each IG vial. Open the vent.
2. Turn the vial upside down and fill the bag with the IG. Repeat this step, if using multiple vials to achieve the desired dose.
3. Remove the filling tube(s) of the bag and place a sterile cap over the open end of the bag and close the clamp on bag.
4. Insert the spike of the administration pump tubing into the bag and fill as directed by your healthcare professional.

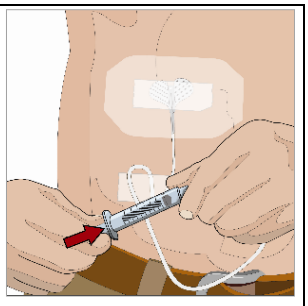
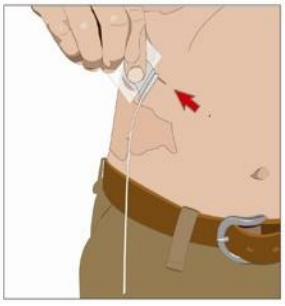
c. If directly from the IG vial:

1. Insert the spike of the vented pump tubing into centre of the stopper of the IG vial(s). Fill the administration pump tubing and set aside until the vorhyaluronidase alfa has been administered.
2. Repeat the steps above for each remaining vial of the IG





9. Prepare the pump: Follow the manufacturer's instructions for preparing the pump.	
10. Prepare the infusion site(s): • Potential sites for infusion include the middle to upper abdomen and thighs. • Avoid: bony prominences, blood vessels, scars, or areas that are inflamed or infected. • If two sites are desired, a bifurcated needle set may be used on opposite sides of the body, for doses above 600 mL • If using three infusion sites, the sites should be at least 10 cm apart • Rotate sites by choosing opposite sides of the body between successive infusions. • Cleanse the infusion site(s) with a sterile alcohol wipe beginning at the centre of each infusion site and moving outward in a circular motion. Allow the infusion site(s) to dry (at least 30 seconds).	 
11. Insert and secure the 24-gauge subcutaneous needle: • Remove the needle cover. Firmly grasp and pinch at least one inch (2 to 2.5 cm) of skin between two fingers. Insert the needle at a 90-degree angle into the subcutaneous tissue and secure the needle with sterile tape. • Check placement: gently pull back on the plunger of attached syringe and monitor for any blood return in the tubing. – If blood is seen in the tubing, remove and discard the needle and repeat steps 3, 5 and 6 with a new subcutaneous needle and infusion site.	90-degree angle to skin 
12. Check the proper needle placement before starting the infusion if instructed by your healthcare professional.	
13. 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.	

14. Administer the vorhyaluronidase alfa of HYQVIA: Administer the entire vorhyaluronidase alfa dose first. If more than one site is used, divide the contents equally between sites. **If using the push method to deliver HY:** • Slowly push the plunger of the smaller syringe with the vorhyaluronidase alfa at an initial rate per infusion site to approximately 1 to 2 mL per minute and increase as tolerated. **If using the pump method to deliver HY:** • If using a pump, prepare the pump to infuse the vorhyaluronidase alfa at an initial rate per infusion site of 60 to 120 mL/hour/site and increase as tolerated. At the end of infusion, disconnect the empty syringe and attach pump tubing/syringe containing the Normal Immunoglobulin of HYQVIA to the same subcutaneous needle set.	
15. Administer the Normal Immunoglobulin of HYQVIA: Within approximately 10 minutes of completing the infusion of the vorhyaluronidase alfa of HYQVIA, start the variable rate program of the infusion pump to initiate the infusion of the full therapeutic dose of Normal Immunoglobulin of HYQVIA. At the end of infusion, flush infusion tubing up to the needle with normal saline or 5% Glucose in water, if directed by your healthcare professional.	
16. Flush the pump tubing when the infusion is complete if instructed by your healthcare professional: If instructed by your healthcare professional, attach a sodium chloride solution bag to the pump tubing/needle set to push the human normal immunoglobulin 10% up to the needle wings.	
17. Remove subcutaneous needle(s) from the infusion site(s): After the infusion is complete, Remove the needle set by loosening the dressings 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.	
18. Document the infusion: Remove the peel-off label from each IG vial of HYQVIA used and affix to the patient's treatment record or infusion log. In addition, record the time, date, dose, infusion site location and any reactions after each infusion. Throw away any unused product in the vial and the disposable supplies as recommended by your healthcare professional. For self-administration, provide the patient with instructions and training for infusion in the home or other appropriate setting.	