1. NAME OF THE MEDICINAL PRODUCT

HyQvia 100 mg/mL solution for infusion for subcutaneous use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HyQvia is a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20).

Human normal immunoglobulin (SCIg)*

One mL contains:
Human normal immunoglobulin. 100 mg
(purity of at least 98% IgG)

Each vial of 25 mL contains: 2.5 g of human normal immunoglobulin.
Each vial of 50 mL contains: 5 g of human normal immunoglobulin.
Each vial of 100 mL contains: 10 g of human normal immunoglobulin.
Each vial of 200 mL contains: 20 g of human normal immunoglobulin.
Each vial of 300 mL contains: 30 g of human normal immunoglobulin.

Distribution of the IgG subclasses (approx. values):
$IgG_1 \geq 56.9\%$
$IgG_2 \geq 26.6\%$
$IgG_3 \geq 3.4\%$
$IgG_4 \geq 1.7\%$

The maximum IgA content is 140 micrograms/mL.

* Produced from the plasma of human donors.

Recombinant human hyaluronidase (rHuPH20)

One mL contains:
Recombinant human hyaluronidase. 160 units

Each vial of 1.25 mL contains: 200 units of recombinant human hyaluronidase.
Each vial of 2.5 mL contains: 400 units of recombinant human hyaluronidase.
Each vial of 5 mL contains: 800 units of recombinant human hyaluronidase.
Each vial of 10 mL contains: 1600 units of recombinant human hyaluronidase.
Each vial of 15 mL contains: 2400 units of recombinant human hyaluronidase.

Excipients with known effects:

- Recombinant human hyaluronidase (rHuPH20)

The rHuPH20 is a purified glycoprotein of 447 amino acids produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

- Sodium (as chloride and as phosphate)

The total sodium content of recombinant human hyaluronidase is 4.03 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

IG 10% is a clear or slightly opalescent and colourless or pale-yellow solution. The solution has a pH of 4.6 to 5.1 and an osmolality of 240 to 300 mOsmol/kg.

rHuPH20 is a clear, colourless solution. The solution has a pH of 6.5 to 8.0 and an osmolality of 290 to 350 mOsmol/kg.

Patient safety information Brochure
The marketing of HyQvia is subject to a risk management plan (RMP) including a 'Patient safety information brochure'. The 'Patient safety information brochure, emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the brochure before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults, children and adolescents (0 to 18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of < 4 g/L.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Immunomodulatory therapy in adults, children, and adolescents (0 to 18 years) in:

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg.

4.2 Posology and method of administration

Therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

The medicinal product should be administered via the subcutaneous (SC) route. The dose and dose regimens are dependent on the indication.

The dose may need to be individualised for each patient dependent on the pharmacokinetic (PK) and clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients. The following dose regimens are given as a guideline.

Posology

Replacement therapy in PID

Patients naïve to immunoglobulin therapy

The dose required to achieve a trough IgG level of 6 g/L is of the order of 0.4 to 0.8 g/kg body weight per month. The dose interval to maintain steady-state levels varies from 2-to-4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher IgG trough levels (> 6 g/L).

At the initiation of therapy, it is recommended that the treatment intervals for the first infusions be gradually prolonged from a 1-week dose to up 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.

Patients previously treated with Intravenous immunoglobulin (IVIg)
For patients switching directly from IVIg, or who have a previous IVIg dose that can be referenced, the medicinal product should be administered at the same dose and at the same frequency as their previous IVIg 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 previously treated with subcutaneous immunoglobulin (SCIg)

The initial dose of the medicinal product is the same as for SCIg treatment but may be adjusted to 3-or 4-weeks interval. The first infusion should be given one week after the last treatment with the previous immunoglobulin.

Replacement therapy in SID

The recommended dose is 0.2 to 0.4 g/kg every 3 to 4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

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.

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 the table 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 1), 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 1: Recommended IVIg to HyQvia infusion dose titration 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.*

On a given infusion day, the maximum infusion volume should not exceed 1200 mL for patients weighing ≥ 40 kg or 600 mL for < 40 kg. Suppose the maximum daily dose limit is exceeded or the patient cannot tolerate the infusion volume. In that case, 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 up to 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.

Paediatric population

Replacement therapy

The dosing schedule for children and adolescents (0 to 18 years) is the same as for adults. The dosing is based on body weight and adjusted to the clinical outcome. Currently, available data are described in sections 4.8, 5.1 and 5.2.

Immunomodulatory therapy

The dosing schedule for children and adolescents (0 to 18 years) is the same as for adults. The dosing is based on the calculated weekly equivalent dose and adjusted to the clinical outcome. Currently, available data are described in sections 4.8, 5.1 and 5.2.

Method of administration

The medicinal product is for subcutaneous use only, do not administer intravenously.

Each vial of IG 10% is supplied with the appropriate corresponding quantity of rHuPH20 (see section 6.5). The full contents of the rHuPH20 vial should be administered regardless of whether the full content of the IG 10% vial is administered.

The 2 components of the medicinal product must be administered sequentially through the same subcutaneous needle beginning with the rHuPH20 followed by IG 10%.

Example: Patient is prescribed 110 grams (g) of HyQvia: This will require 3 vials of 30 g and 1 vial of 20 g for the total dose of 110 g/1100 mL of the IG 10% component of HyQvia. The volume of rHuPH20 will be (3 x 15 mL + 1 x10 mL) = 55 mL. If the dose is greater than 120 g, HyQvia 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).

Infusion site leakage can occur during or after subcutaneous administration of immunoglobulin, including HyQvia. Consider using longer needles (12 mm or 14 mm) and/or more than one infusion site. Any change of needle size would have to be supervised by the treating physician.

Home-treatment

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

HyQvia can be administered in a full therapeutic dose at up to 3 infusion sites up to every 4-weeks. Adjust the frequency and number of infusion sites, considering volume, total infusion time, and tolerability so that the patient receives the same weekly equivalent dose. If a patient misses a dose, administer the missed dose as soon as possible and then resume scheduled treatments as applicable.

Device-assisted infusion

The IG 10% component should be infused using a pump. The rHuPH20 may be hand-pushed 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 rHuPH20 vial size use an 18-to 22-gauge needle to withdraw the contents of the vial to prevent stopper push through or coring; for all other vial sizes a needle or needleless device may be used to withdraw the contents of the vial.

Infusion site

The suggested site(s) for the infusion of the medicinal product are the middle to upper abdomen and thighs. If 2 sites are used, the 2 infusion sites should be on contra lateral sides of the body. If using three infusion sites, the sites should be at least 10 cm apart. Avoid bony prominences, or scarred areas. The product should not be infused at or around an infected or acutely inflamed area due to the potential risk of spreading a localised infection. Avoid at least 5 cm away from the umbilicus.

Infusion rate

It is recommended that the rHuPH20 component be administered at a constant rate and that the rate of administration of the IG 10% should not be increased above the recommended rates, particularly when the patient has just started with HyQvia therapy.

First, the full dose of rHuPH20 solution is infused at a rate of 1 to 2 mL/minute (or 60 mL/hr to 120 mL/hr) per infusion site or as tolerated. Within 10 minutes of the rHuPH20, start the infusion of the full dose per site of IG 10% through the same subcutaneous needle set.

The following infusion rates of the IG 10% are recommended per infusion site.

Table 2 : The recommended infusion rates of the IG 10% per infusion site

	Subjects < 40 kg		**Subjects ⩾ 40 kg**	
Interval/ Minutes	First 2 infusions (mL/hour/infusion site)	Subsequent 2 to 3 infusions (mL/hour/infusion site)	First 2 infusions (mL/hour/infusion site)	Subsequent 2 to 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

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.

For instructions on the handling and preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

HyQvia must not be given intravenously or intramuscularly.

Hypersensitivity to the active substance (IgG) or to any of the excipients listed in section 6.1 (see section 4.4).

Hypersensitivity to human immunoglobulins, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA.

Known systemic hypersensitivity to hyaluronidase or rHuPH20.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use

If HyQvia is accidentally administered into a blood vessel, patients could develop shock.

The recommended infusion rate given in section 4.2 should be adhered to. Patients must be closely monitored throughout the infusion period, particularly patients starting with therapy.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Potential complications can often be avoided by:

- initially infusing the product slowly (see section 4.2).
- ensuring that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative immunoglobulin product or when there has been a long interval since the previous

infusion should be monitored during the first infusion and for the first hour after the first infusion, to detect potential adverse signs.

All other patients should be observed for at least 20 minutes after the administration.

When treatment is given at home, support from another responsible person should be available for treating adverse reactions or to summon help should a serious adverse reaction occur. Patients on self-home treatment and/or their guardian should also be trained to detect early signs of hypersensitivity reactions.

In case of adverse reaction, either the rate of administration must be reduced, or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction. In case of shock, immediately discontinue the infusion and treat the patient for shock.

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.

Hypersensitivity to IG 10%

True hypersensitivity reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with SCIg products remains the only option, should be treated with HyQvia only under close medical supervision.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

- If a patient is at high risk for any allergic reactions, the medicinal product should be administered only where supportive care is available for life threatening reactions.
- Patients should be informed of the early signs of anaphylaxis/hypersensitivity (hives, pruritus, generalised urticaria, tightness of the chest, wheezing, and hypotension).
- Depending on the severity of associated reaction, and medical practice, pre-medication may prevent this type of reaction.
- If known anaphylactic or severe hypersensitivity to human immunoglobulin exists, it should be noted in the patient records.

Hypersensitivity to rHuPH20

Any suspicion of allergic or anaphylactic like reactions following rHuPH20 administration requires immediate discontinuation of the infusion and standard medical treatment should be administered, if necessary.

Immunogenicity of rHuPH20

Development of non-neutralizing antibodies and 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, 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 (see section 4.8).

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before using immunoglobulins. Caution should be exercised in patients with pre-existing risk factors for thromboembolic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolaemic patients, patients with diseases which increase blood viscosity). Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. Thrombosis may also occur in the absence of known risk factors.

Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms.

Haemolytic anaemia

Immunoglobulin products contain antibodies to blood groups (e.g. A, B, D) which may act as haemolysins. These antibodies bind to red blood cells (RBC) epitopes (which may be detected as a positive direct antiglobulin test [DAT, (Coombs' test)] and, rarely, may cause haemolysis. Immunoglobulin product recipients should be monitored for clinical signs and symptoms of haemolysis.

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg and SCIg treatment; the symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about the first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, 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) IVIg treatment. From post-marketing data no clear correlation of AMS to higher doses was observed. Higher incidences of AMS were seen in women.

Interference with serological testing

After infusion of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte´s surface 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 immunoglobulin products may lead to false positive readings in assays that depend on detection of β-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

Transmissible agents

Human normal immunoglobulin and human serum albumin (stabilizer of the rHuPH20) are produced from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the 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 infectious

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 virus (HCV), and for the non-enveloped hepatitis A (HAV) and parvovirus B19 viruses.

There is reassuring clinical evidence regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to viral safety.

Sodium content

The IG 10% component is essentially sodium-free. The rHuPH20 contains the following amount (mg) of sodium per vial:

1.25 mL contains 5.0 mg of sodium.
2.5 mL contains 10.1 mg of sodium.
5 mL contains 20.2 mg of sodium.
10 mL contains 40.3 mg of sodium.
15 mL contains 60.5 mg of sodium.

This is equivalent to 0.25 to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

The listed warnings and precautions apply both to adults and children.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

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 medicinal 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.

Paediatric population

The listed interactions apply both to adults and children.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical studies and therefore should only be given with caution to pregnant women and breast-feeding mothers.

Nine women ever treated with HyQvia were enrolled in a prospective, uncontrolled, multicentre post-authorisation Pregnancy Registry (Study 161301). Of the 8 pregnancies with known outcomes, there were 8 live births with normal APGAR scores. There were no specified labour or delivery complications. No adverse events were reported as related to this medicinal product. Four (4) mothers were tested for anti-rHuPH20 binding, or neutralizing antibodies and no antibodies were detected.

Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Development and reproductive toxicology studies have been conducted with rHuPH20 in mice and rabbits. No adverse reactions on pregnancy and foetal development 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 this medicinal product on the human embryo or on human foetal development are currently unknown (see section 5.3).

Breast-feeding

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry. One infant in the Pregnancy Registry (Study 161301) was breastfed. All adverse events were reported as not related to previous or current HyQvia treatment.

Fertility

There are currently no clinical safety data for this medicinal product on fertility available.

Clinical experience with immunoglobulins suggests that no harmful effects of IG 10% on fertility are to be expected.

Animal studies do not indicate direct or indirect harmful effects of rHuPH20 with respect to reproductive potential at the doses used for facilitating administration of IG 10% (see section 5.3).

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions e.g., dizziness (see section 4.8) associated with this medicinal product. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

IG 10%

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

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Local reactions at infusion sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash, may frequently occur.

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.

Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis have been rarely observed with IVIg and SCIg products.
For safety with respect to transmissible agents, see section 4.4.

rHuPH20

The most frequent adverse reactions reported during post-marketing use of rHuPH20 in similar formulations administered subcutaneously for the dispersion and absorption of subcutaneously administered fluids or medicinal products have been mild local infusion site reactions such as erythema and pain. Oedema has been reported most frequently in association with large volume subcutaneous fluid administration.

Antibodies against rHuPH20

A total of 13 out of 83 subjects who participated in pivotal PID study developed an antibody capable of binding to rHuPH20 at least once during the clinical study. These antibodies were not capable of neutralizing rHuPH20. No temporal association between adverse reactions and the presence of anti-rHuPH20 antibodies could be demonstrated. There was no increase in incidence or severity of adverse reactions in patients who developed antibodies to rHuPH20.

A total of 16 out of 132 patients who received rHuPH20 developed anti-rHuPH20 binding antibodies at least once in CIDP studies that included 289 patient-years of follow-up. Two subjects developed anti- rHuPH20 neutralizing antibodies. No efficacy or safety issues were identified with binding or neutralizing antibody positivity.

Tabulated list of adverse reactions

The safety of HyQvia was evaluated in 228 patients who received a total of 7 287 infusions across 6 clinical studies. It included 4 clinical studies (160602, 160603, 160902, and 161101) in 124 patients with PID, who received 3 202 infusions, and 2 clinical studies (161403 Epoch 1 and 161505) in 104 patients with CIDP, who received 4 085 HyQvia infusions.

The table presented below is according to the MedDRA (27.1) System Organ Classification (SOC and Preferred Term Level).

Frequencies have been evaluated using the following convention: 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), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Frequency of Adverse drug reactions (ADR) per infusion reported in patients treated with HyQvia in clinical studies (160602, 160603, 160902,161101, 161403 Epoch 1 and 161505) and post-marketing surveillance, reporting rate per patient or per infusion.

MedDRA System Organ Class (SOC)	**Adverse drug reactions**	**Frequency per patient N=228**	**Frequency per infusion N=7,287**
Infections and Infestations	Meningitis aseptic*	Not Known	Not Known
Immune System disorders	Hypersensitivity*	Not Known	Not Known
Nervous system disorders	Headache	Very Common	Common
	Dizziness	Common	Uncommon
	Migraine	Common	Uncommon
	Paraesthesia	Common	Uncommon
	Burning sensation	Common	Uncommon
	Tremor	Common	Rare
	Cerebrovascular accident and Ischaemic stroke	Uncommon	Rare
Cardiac disorders	Sinus tachycardia and Tachycardia	Common	Uncommon

MedDRA System Organ Class (SOC)	Adverse drug reactions	Frequency per patient N=228	Frequency per infusion N=7,287
Vascular disorders	Hypertension and Blood pressure increased	Very Common	Uncommon
	Hypotension	Common	Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common	Rare
Gastrointestinal disorders	Nausea	Very Common	Common
	Abdominal pain, Abdominal pain lower, Abdominal pain upper and Abdominal tenderness	Very Common	Uncommon
	Diarrhoea	Very Common	Uncommon
	Vomiting	Very Common	Uncommon
	Abdominal distension	Common	Uncommon
Skin and subcutaneous tissue disorders	Erythema	Common	Uncommon
	Pruritus	Common	Uncommon
	Rash, Rash erythematous, Rash macular, Rash maculo-papular and Rash papular	Common	Uncommon
	Urticaria	Common	Uncommon
	Hyperhidrosis	Common	Rare
Musculoskeletal and connective tissue disorders	Myalgia	Common	Uncommon
	Arthralgia	Very Common	Uncommon
	Limb discomfort and Pain in extremity	Common	Uncommon
	Back pain	Common	Uncommon
	Joint stiffness	Uncommon	Uncommon
	Musculoskeletal chest pain	Common	Uncommon
	Groin pain	Common	Rare
Renal and urinary disorders	Haemosiderinuria	Common	Rare
General disorders and administration site conditions	Local reactions (Total)	Very Common	Very Common
	- Infusion site discomfort, Infusion site pain, Injection site pain, Puncture site pain and Tenderness	Very Common	Common
	- Infusion site erythema and Injection site erythema	Very Common	Common
	- Infusion site oedema, Injection site oedema, Infusion site swelling, Injection site swelling and Swelling (local)	Very Common	Common
	- Infusion site pruritus, Injection site pruritus, Puncture site pruritus and Vulvovaginal pruritus	Very Common	Common
	- Infusion related reaction	Common	Uncommon
	- Infusion site bruising, Injection site bruising, Infusion site haematoma, Injection site haematoma, Infusion site haemorrhage and Vessel puncture site bruise	Common	Uncommon

MedDRA System Organ Class (SOC)	Adverse drug reactions	Frequency per patient N=228	Frequency per infusion N=7,287
	- Infusion site reaction, Injection site reaction and Puncture site reaction	Common	Uncommon
	- Infusion site mass, Injection site mass and Infusion site nodule	Common	Uncommon
	- Infusion site discoloration	Common	Uncommon
	- Infusion site rash and Injection site rash	Common	Uncommon
	- Infusion site induration and Injection site induration	Common	Uncommon
	- Infusion site warmth	Common	Rare
	- Infusion site paraesthesia and Injection site paraesthesia	Common	Rare
	- Infusion site inflammation	Common	Rare
	- Infusion site leakage*	Not Known	Not Known
	Feeling hot and Pyrexia	Very Common	Common
	Influenza-like illness*	Not Known	Not Known
	Asthenia, Fatigue, Lethargy and Malaise	Very Common	Common
	Chills	Common	Uncommon
	Oedema, Oedema peripheral and Swelling (systemic)	Common	Uncommon
	Localised oedema, Peripheral swelling and Skin oedema	Common	Uncommon
	Gravitational oedema, Oedema genital, Scrotal swelling and Vulvovaginal swelling	Common	Uncommon
Investigations	Coombs direct test positive and Coombs test positive	Common	Rare

***** Adverse events from post-marketing surveillance.

Description of selected adverse reactions

The most common local reactions observed during the pivotal clinical studies include infusion site pain, infusion site erythema and infusion site oedema. Most of the local reactions were mild in severity and self-limited. In the PID studies, 2 instances of local adverse reactions were severe (infusion site pain and infusion site swelling) and in the CIDP studies 4 instances were severe (infusion site extravasation, infusion site inflammation, infusion site pruritus and infusion site reaction). In the PID studies, there were 2 instances of transient genital oedema, one considered severe, that resulted from diffusion of the medicinal product from the infusion site in the abdomen. In the CIDP studies there was one mild instance of genital oedema (penile swelling). No skin changes were observed that did not resolve during the clinical study.

Paediatric population

PID

In the pivotal study 160603 there were 2 of the 24 paediatric patients with total anti-rHuPH20 antibody levels at or above 1:160. None had neutralising antibodies.

A prospective, Phase 4, multicentre study in Europe evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy (Study 161504). No new safety concerns

were identified. No subject was positive (titre ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PIDD.

Results of clinical studies indicate similar safety profiles in adults and paediatric population, including the nature, frequency, seriousness and reversibility of adverse reactions.

CIDP

HyQvia has not been evaluated in clinical studies in children or adolescent patients (0 to 18 years) with CIDP.

Elderly Patients

Primary Immunodeficiency

Post-authorisation safety studies (EU 161302, US 161406) included 15 and 77 elderly subjects, respectively. Overall, no significant safety differences were observed between PID subjects above 65 years and those between 18 and 65 years old.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

The consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration, ATC code: J06BA01

Mechanism of action

The IG 10% component provides the therapeutic effect of this medicinal product. The rHuPH20 facilitates the dispersion and absorption of IG 10%.

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of opsonising and neutralizing antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled human plasma from not fewer than 1 000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated but includes immunomodulatory effects.

Recombinant human hyaluronidase is a soluble recombinant form of human hyaluronidase that increases the permeability of the subcutaneous tissue by temporarily depolymerising hyaluronan. Hyaluronan is a polysaccharide found in the intercellular matrix of the connective tissue. It is depolymerised 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 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 efficacy and safety

PID

Efficacy and safety of HyQvia was assessed in a phase 3 study (160603) in 83 patients with PID. Patients were treated with it at either 3- or 4-week treatment intervals for a total of 12-months (following a brief titration period). The dose was based on the previous treatment with intravenous IG 10% (320 to 1 000 mg/kg body weight /4-weeks) and was individually adapted, ensuring adequate IgG levels throughout the study.

The results of the study showed a rate of validated, acute, serious bacterial infections per year during HyQvia treatment of 0.025 (upper limit of the one-sided 99% confidence interval 0.046). The overall rate of infections was less during HyQvia administration than during the 3-months intravenous administration of IG 10%: the point estimate of the annualized rate of all infections was 2.97 (95% CI: 2.51 to 3.47) for HyQvia and 4.51 (95% CI: 3.50 to 5.69) for intravenous IG 10% infusions.

Nearly all of the subjects were able to attain the same dose interval with HyQvia as they had for intravenous administration. Seventy-eight (78) of 83 (94%) subjects attained the same 3- or 4-week dosing whereas one decreased from 4-to 3-weeks, one from 4-to 2-weeks and one from 3-to 2-weeks (2-subjects withdrew during the titration period).

The median number of infusion sites per month for HyQvia was 1.09, which is slightly lower than the median number of intravenous IG 10% infusion sites used in this study (1.34), and considerably lower than the median number of infusion sites in the study of subcutaneous administration of IG 10% (21.43).

Sixty-six (66) patients who completed the pivotal phase 3 study participated in an extension study (160902) for the evaluation of long-term safety, tolerability, and efficacy of HyQvia in PID. The overall combined exposure of PID patients in both studies was 187.69 patient years; the longest exposure for adults was 3.8-years and 3.3-years for paediatric patients.

Study 161302 (EU):

This non-interventional post-authorisation safety study on the long-term safety of HyQvia in subjects treated with HyQvia was carried out for approximately 6 years. A total of 111 adult subjects were enrolled in the study. The mean age of the study population was 46.2 (standard deviation [SD]=14.69) years, and 14.2% (n=15) of the subjects were 65 years or older. Over half of the subjects were female (n=60, 56.6%), of whom 56.7% were of childbearing potential This study confirms the known safety profile of HyQvia.

Study 161406 (US):

This non-interventional post-authorisation safety study on the long-term safety of HyQvia was carried out for approximately 6 years. A total of 253 adult subjects with PID were enrolled. The median age was 57.0 years, 30.4% (n=77) were 65 years or older, and 79.1% (n=200) were female, 22.5% (n=45) of whom were of childbearing potential. This study confirms the known safety profile of HyQvia.

CIDP

Study 161403 (ADVANCE-1):

In a multicentre, randomized, placebo-controlled, phase 3 study, 132 adult subjects with CIDP underwent evaluation of the efficacy, safety, and tolerability of HyQvia as a maintenance therapy to prevent relapse that allows self-infusion of a total therapeutic dose every 2- to 4-weeks.

The study enrolled subjects ≥ 18 years of age (male or female) at the time of screening who had a documented diagnosis of definite or probable CIDP as per the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria. All eligible subjects had responded to IgG treatment in the past (partial or complete resolution of neurological symptoms and deficits) and were on a stable dose of 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. 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 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.

Study 161505 (ADVANCE-3):

Study 161505 was a Phase 3b, long-term, multicentre study of HyQvia subcutaneous treatment in adult subjects with CIDP who had received prior HyQvia therapy (or placebo) in Study 161403. The primary objective of the study was to collect long-term data on the safety, tolerability, and efficacy (as exploratory measures only) of HyQvia in the subject population. Enrollment into this study was open to subjects who completed Study 161403 Epoch 1 without CIDP worsening. A total of 85 subjects who completed Study 161403 and met the selection criteria for Study 161505 were enrolled and treated. The mean duration of exposure to HyQvia was 31.1 months (range: 0 to 77.3). The total exposure time was 219.9 patient-years. The safety outcomes confirmed the known safety profile of HyQvia and did not reveal any new safety concerns. A total of 10 subjects of the 77 evaluable subjects developed a CIDP relapse during the study. The 6-month and annual relapse rates were 0.023 and 0.045, respectively.

Paediatric population

PID

In the pivotal studies, HyQvia was evaluated in 24 paediatric patients, including 13 patients between 4 and < 12 years and 11 between 12 and < 18 years, who were treated for up to 3.3-years with an overall safety experience equivalent to 48.66 patient years (as described in section Clinical efficacy and safety). No appreciable differences in the pharmacodynamic effects or efficacy and safety of HyQvia were observed between paediatric patients and adults. See sections 4.2 and 4.8.

The medicinal product was evaluated in 42 paediatric subjects (age 2 to <18 years), in a Phase 4, non-controlled, multicentre study in paediatric subjects who had received prior immunoglobulin therapy. No new safety concerns were identified in paediatric subjects with PID.

CIDP

HyQvia has not been evaluated in clinical studies in children or adolescent patients (0 to 18 years) with CIDP.

5.2 Pharmacokinetic properties

Following subcutaneous administration of HyQvia in PID patients, peak serum IgG levels are achieved in the recipient's circulation after approximately 3 to 5 days.
IgG and IgG complexes are broken down in cells of the reticuloendothelial system.

PID

The pharmacokinetics (PK) of HyQvia were evaluated in a clinical study (160601, 160602 and 160603) in patients with PID aged 12 years and older. Data from the PID clinical studies show that serum IgG trough levels can be maintained by dosing regimens of 320 to 1 000 mg/kg body weight/4-weeks given at intervals of 3- or 4-weeks.

The pharmacokinetic results are presented in the table below, as compared to data for intravenous administration of IG 10% obtained in the same study.

Table 4: Pharmacokinetic Parameters of HyQvia Compared to Intravenous Administration of IG 10%

Parameter	**HyQvia Median (95% CI) N=60**	**IVIG 10% Median (95% CI) N=68**
C_{max} [g/l]	15.5 (14.5; 17.)	21.9 (20.7; 23.9)
C_{min} [g/l]	10.4 (9.4 to 11.2)	10.1 (9.5 to 10.9)
AUC per week [g*days/l]	90.52 (83.8 to 9)	93.9 (89.1 to 102.1)
T_{max} [days]	5.0 (3.3 to 5.1)	0.1 (0.1 to 0.1)
Apparent clearance or clearance [mL/kg/day]	1.6 (1.4 to 1.79)	1.4 (1.2 to 1.4)
Terminal half-life [days]	45.3 (41.0 to 60.2)	35.7 (32.4 to 40.4)

CIDP

The complete pharmacokinetic profile of HyQvia was not evaluated in the clinical study (161403) in patients with CIDP aged 18 years and older. Only the serum trough levels of total IgG were assessed throughout the study. Overall, during the treatment periods with HyQvia, serum trough levels of total IgG remained stable. For subjects who developed a relapse and switched to IVIg (n=6), the serum trough levels of total IgG also appeared stable throughout the treatment periods on HyQvia or IVIg.

The median serum trough levels of total IgG in CIDP were approximately 40% greater than in PID.

Paediatric population

PID

In the clinical study with HyQvia, no differences in the plasma IgG trough levels were observed between adult and paediatric patients.

CIDP

HyQvia has not been evaluated in clinical studies in children or adolescent patients (0 to 18 years) with CIDP.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body.

The safety of IG 10% has been demonstrated in several non-clinical studies. Non-clinical data reveal no special risk for humans based on conventional studies of safety pharmacology and toxicity. Studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction in animals are impracticable due to induction of and interference by developing antibodies to heterologous proteins.

Long term animal studies to evaluate the carcinogenic or mutagenic potential of rHuPH20 have not been conducted. No adverse reactions on fertility were observed in mice, rabbits and cynomolgus

monkeys exposed to antibodies that bind to rHuPH20 and species-specific hyaluronidase. 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 rHuPH20 on human fertility are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human normal immunoglobulin (IG 10%) vial

Glycine
Water for injection

Recombinant human hyaluronidase (rHuPH20) vial

Sodium chloride
Sodium phosphate dibasic dihydrate
Sodium hydroxide
Human serum albumin, 25%
Edetate disodium dihydrate (EDTA)
Calcium chloride dihydrate
25% Hydrochloric acid
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

The product may be stored at temperatures above +8°C and below +25°C for up to 3 months. Do not refrigerate after storing at room temperature. Discard after 3 months or after the expiry date is reached whichever occurs sooner.

The date of removal from the refrigerator should be recorded on the outer carton.

Do not freeze.

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

6.5 Nature and contents of container

Human normal immunoglobulin (IG 10%) vial

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

Recombinant human hyaluronidase (rHuPH20) 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 IG 10% and one vial of rHuPH20 in a dual vial unit.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The medicinal product should be brought to room temperature before use. Do not use heating devices including microwaves.

IG 10% is a clear or slightly opalescent and colourless or pale-yellow solution. rHuPH20 is a clear, colourless solution.

This medicinal product is comprised of 2 vials. Both vials should be inspected visually for particulate matter and discoloration prior to administration. Solutions that are cloudy or have deposits should not be used.

Do not shake.

Do not mix the components of HyQvia prior to administration.

Do not use vented vial access devices to remove rHuPH20 from vials.

Use aseptic technique when preparing and administering HyQvia. In cases where more than one vial of the medicinal product IG 10% or rHuPH20 is required to obtain the required dose of the infusion, the IG 10% and/or rHuPH20 should be prepared separately in appropriate solution containers before administration. Partially used vials should be discarded.

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

7. License Holder and Importer:

Takeda Israel Ltd., 25 Efal st., P.O.B 4140, Petach Tikva 4951125

8. Registration number:

160-21-35267-00

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