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.

Excipients with known effects:

- Recombinant human hyaluronidase (rHuPH20)
  Recombinant human hyaluronidase 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 (infusion).

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

Recombinant human hyaluronidase is a clear, colourless solution. The solution has a pH of 6.5-8.0 and an osmolality of 290-350 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients.
- Hypogammaglobulinaemia in patients pre- and post-allogeneic hematopoietic stem cell transplantation (HSCT).

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dose regimen are dependent on the indication.
The medicinal product should be administered via the subcutaneous route.

In replacement therapy the dose may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients The following dosage regimens are given as a guideline.

Replacement therapy

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

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 dosage and aim for higher 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 immunoglobulin administered intravenously
For patients switching directly from intravenous administration of immunoglobulin, 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 previously treated with immunoglobulin administered subcutaneously
For patients currently being administered immunoglobulin subcutaneously, the initial dose of HyQvia is the same as for subcutaneous treatment, but may be adjusted to 3- or 4-weeks interval. The first infusion of HyQvia should be given one week after the last treatment with the previous immunoglobulin.

Paediatric population

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned condition. 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.
- Visually inspect both components of HyQvia for discoloration and particulate matter prior to administration.
- Allow refrigerated product to come to room temperature before use. Do not use heating devices including microwaves.
- Do not shake.
- This medicinal product is comprised of two vials. Do not mix the components of this medicinal product.

Each vial of IG 10% is supplied with the appropriate corresponding quantity of recombinant human hyaluronidase as stated in the table below. The full contents of the recombinant human hyaluronidase vial should be administered regardless of whether the full content of the IG 10% vial is administered. The two components of the medicinal product must be administered sequentially through the same needle beginning with the recombinant human hyaluronidase followed by IG 10%, as described below.

HyQvia administration scheme		
Recombinant human hyaluronidase	**Human normal immunoglobulin 10%**	
Volume (mL)	**Protein (grams)**	**Volume (mL)**
1.25	2.5	25
2.5	5	50
5	10	100
10	20	200
15	30	300

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. Any change of needle size would have to be supervised by the treating physician.

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 will 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 used to administer a full therapeutic dose in one to two sites up to every four weeks. Adjust the frequency and number of infusion sites taking into consideration volume, total infusion time, and tolerability so that the patient receives the same weekly equivalent dose. If a patient misses a

dose, administer the missed dose as soon as possible and then resume scheduled treatments as applicable.

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 recombinant human hyaluronidase vial size use a 18-22 gauge needle to withdraw the contents of the vial to prevent stopper push through or coring; for all other vial sizes a needle or needle-less device may be used to withdraw the contents of the vial.

The suggested site(s) for the infusion of the medicinal product are the middle to upper abdomen and thighs. If two sites are used, the two infusion sites should be on contra lateral sides of the body. 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 localized infection.

It is recommended that the recombinant human hyaluronidase 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 recombinant human hyaluronidase solution is infused at a rate of 1 to 2 ml/minute per infusion site or as tolerated. Within 10 minutes of the recombinant human hyaluronidase ,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:

	Subjects < 40 kg		**Subjects ⩾ 40 kg**	
Interval/Minutes	First Two Infusions (mL/hour/infusion site)	Subsequent 2-3 Infusions (mL/hour/infusion site)	First Two Infusions (mL/hour/infusion site)	Subsequent 2 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 how to use the medicinal product, 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 recombinant human hyaluronidase.

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.

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, in order 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 subcutaneous IgG 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 patient is at high risk for any allergic reactions, the 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, generalized 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 recombinant human hyaluronidase

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

Immunogenicity of recombinant human hyaluronidase

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

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 use of 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 hypovolemic 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.

Acute renal failure

Severe renal adverse reactions have been reported in patients receiving immunoglobulin intravenous treatment, particularly those products containing sucrose (HyQvia does not contain sucrose).

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with intravenous and subcutaneous immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about 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) intravenous immunoglobulin treatment. From post-marketing data no clear correlation of AMS to higher doses was observed. Higher incidences of AMS were seen in women.

Important information about some of the ingredients of HyQvia

This medicinal product does not contain sugars.

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 recombinant human hyaluronidase) 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 the viral safety.

Sodium content

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

1.25 mL – 5.0 mg
2.5 mL – 10.1 mg
5 mL – 20.2 mg
10 mL – 40.3 mg

15 mL – 60.5 mg

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 trials 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, multicenter post-authorization Pregnancy Registry (Study 161301). Of the 8 pregnancies with known outcomes, there were 8 live births with normal APGAR scores. There were no specified labor or delivery complications. No adverse events were reported as related to HyQvia. Four 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 recombinant human hyaluronidase in mice and rabbits. No adverse effects on pregnancy and foetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to recombinant human hyaluronidase were transferred to offspring in utero. The effects of antibodies to the recombinant human hyaluronidase component of HyQvia 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 HyQvia 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 recombinant human hyaluronidase 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

HyQvia has no or negligible influence on the ability to drive and use machines, e.g. dizziness (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions (ARs) of HyQvia were local reactions. The most frequently reported systemic ARs were headache, fatigue and pyrexia. The majority of these ARs were mild to moderate.

Human normal immunoglobulin

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 hemolytic 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 IV and SC administration of immunoglobulin products.

Recombinant human hyaluronidase

The most frequent adverse reactions reported during post-marketing use of recombinant human hyaluronidase 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 recombinant human hyaluronidase

A total of 13 out of 83 subjects who participated in pivotal study developed an antibody capable of binding to recombinant human hyaluronidase (rHuPH20) at least once during the clinical study. These antibodies were not capable of neutralizing recombinant human hyaluronidase. 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 recombinant human hyaluronidase.

Tabulated list of adverse reactions

The safety of HyQvia was evaluated in 4 clinical studies (160602, 160603, 160902, and 161101) in 124 unique patients with PID receiving 3,202 infusions.

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

Frequencies per infusion 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.

Frequency of Adverse Reactions (ADRs) with HyQvia				
MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Rare
Gastrointestinal disorders		Vomiting, nausea, abdominal pain (including abdominal upper and lower pain and tenderness), diarrhoea	Abdominal distension	

General disorders and administration site conditions	Local reactions (total) [a]: Infusion site pain (including discomfort, tenderness, groin pain)	Local reactions (total): Infusion site erythema, infusion site swelling (including local swelling and oedema), infusion site pruritus (including vulvovaginal pruritus) Pyrexia, asthenic conditions (including asthenia, fatigue, lethargy, malaise)	Local reactions (total): Infusion site discoloration, infusion site bruising (including hematoma, haemorrhage), infusion site mass (including nodule), infusion site warmth, infusion site induration, gravitational oedema/genital swelling[b] (including genital oedema, scrotal and, vulvovaginal swelling) Oedema (including peripheral, swelling), chills, hyperhidrosis	Burning sensation
Investigations			Direct Coombs' test positive	
Musculoskeletal and connective tissue disorders		Myalgia, musculoskeletal chest pain	Arthralgia, back pain, pain in extremity	
Nervous system disorders		Headache	Migraine dizziness	Paresthesia
Skin and subcutaneous tissue disorders			Erythema, rash (including erythematous, papular, maculo-papular), pruritus, urticaria	
Vascular disorders			Hypertension, blood pressure increase	
Renal and urinary disorders				Hemosiderinuria

[a] The following ADRs are not listed but also calculated in the frequency for Local reactions: feeling hot, infusion site paresthesia.
[b] Gravitational oedema/genital swelling was observed subsequent to lower abdominal quadrants administration.

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience (frequency of these reactions is not known (cannot be estimated from the available data)):

Infections and infestations: Meningitis aseptic

Immune system disorders: Hypersensitivity
General disorders and administration site conditions: Influenza-like illness, infusion site leakage

In addition to the adverse reactions listed above, the following additional adverse reactions have been reported for subcutaneously administered immunoglobulin products:

Anaphylactic shock, anaphylactic/anaphylactoid reaction, tremor, tachycardia, hypotension, flushing, pallor, peripheral coldness, dyspnea, paraesthesia oral, swelling face, dermatitis allergic, musculoskeletal stiffness, injection site urticaria, injection site rash, alanine aminotransferase increased.

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 the medicinal product from the infusion site in the abdomen. No skin changes were observed that did not resolve during the clinical study.

Paediatric population

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

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

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (human normal immunoglobulin): immune sera and immunoglobulins: immunoglobulins, normal human, ATC code: J06BA01

Mechanism of action

The IG 10% component provides the therapeutic effect of this medicinal product. The recombinant human hyaluronidase 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.

Recombinant human hyaluronidase is a soluble recombinant form of human hyaluronidase that increases the permeability of the subcutaneous tissue by temporarily depolymerizing

hyaluronan. Hyaluronan is a polysaccharide found in the intercellular matrix of the connective tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a very fast turnover with half-life of approximately 0.5 days. The recombinant human hyaluronidase 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

Efficacy and safety of HyQvia was assessed in a phase 3 study (160603) in 83 patients with PID. Patients were treated with HyQvia at either 3- or 4-week treatment intervals for a total of 12 months (following a brief titration period). The dose of HyQvia 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 three 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).

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.

Paediatric population

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.

5.2 Pharmacokinetic properties

Following subcutaneous administration of HyQvia, peak serum IgG levels are achieved in the recipient's circulation after approximately 3 to 5 days.

Data from the clinical trials of HyQvia 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 pharmacokinetics of HyQvia were evaluated in a clinical study in patients with PID aged 12 years and older. The pharmacokinetic results are presented in the table below, as compared to data for intravenous administration of IG 10% obtained in the same study.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

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)

Paediatric population

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

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 recombinant human hyaluronidase have not been conducted. No adverse effects on fertility were observed in mice, rabbits and cynomolgus monkeys exposed to antibodies that bind to recombinant human hyaluronidase 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 recombinant human hyaluronidase on human fertility are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human normal immunoglobulin (IG 10%) vial
Glycine
Water for injections

Recombinant human hyaluronidase (rHuPH20) vial
Sodium chloride
Sodium phosphate dibasic
Human albumin, 25%
Edetate disodium
Sodium hydroxide
Calcium chloride

Hydrochloric acid
Water for injections

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).
Do not freeze.
Keep the vials in the outer carton in order to protect 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 recombinant human hyaluronidase in a dual vial unit.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The 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. Recombinant human hyaluronidase is a clear, colourless solution.

The 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 recombinant human hyaluronidase from vials.

Use aseptic technique when preparing and administering HyQvia. In cases where more than one vial of the medicinal product IG 10% or recombinant human hyaluronidase is required to obtain the required dose of the infusion, the IG 10% and/or recombinant human hyaluronidase 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. Marketing Authorization Holder:

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

8. Manufacturer

Baxalta Belgium Manufacturing SA , Belgium
Boulevard René Branquart 80, B-7860 Lessines, Belgium

9. Registration number:

160-21-35267-00

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