

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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):

IgG₁ ≥ 56.9%

IgG₂ ≥ 26.6%

IgG₃ ≥ 3.4%

IgG₄ ≥ 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).
- 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

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 in primary immunodeficiency syndromes (as defined in 4.1)

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.

Secondary immunodeficiencies (as defined in 4.1.)

The recommended dose is 0.2-0.4 g/kg every three to four 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.

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:

| Interval/Minutes | Subjects < 40 kg | | Subjects ≥ 40 kg | |
|-----------------------|---------------------------------------------|--------------------------------------------------|---------------------------------------------|-----------------------------------------------------|
| | 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 mm³, 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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) | <u>Very common</u> | <u>Common</u> | <u>Uncommon</u> | <u>Rare</u> |
| 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

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 (titer ≥ 160) for binding anti-rHuPH20 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.

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. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in Appendix V**.

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

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.

HyQvia was evaluated in 42 pediatric subjects (age 2 to <18 years), in a Phase 4, non-controlled, multicenter study in pediatric subjects who had received prior immunoglobulin therapy. No new safety concerns were identified following HyQvia treatment in pediatric subjects with PIDD.

The European Medicines Agency has deferred the obligation to submit the results of studies with HyQvia in one or more subsets of the paediatric population in treatment of primary immunodeficiency as model for replacement therapy. See section 4.2 for information on paediatric use.

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

Ethylenediaminetetraacetic acid (EDTA) disodium

Calcium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

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

3 years.

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 AUTHORISATION HOLDER

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna, Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/840/001
EU/1/13/840/002
EU/1/13/840/003
EU/1/13/840/004
EU/1/13/840/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 May 2013
Date of renewal: 8 Jan 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE(S)
AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance(s)

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

Name and address of the manufacturers responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorization and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch (where applicable) or use of HyQvia in each Member State the MAH must agree about the content and format of the programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials are aimed at ensuring the appropriate sequence of administration of HyQvia and its excipients, to mitigate the risk of drug administration error in patients who participate in home administration.

The MAH shall ensure that in each Member State where HyQvia is marketed, all health care professionals and patients who are expected to use HyQvia have access to/are provided with the following educational material:

- **Physician educational material**
- **Patient information pack**

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals (HCP)

Guide for Healthcare Professionals (HCPs):

- Information on HyQvia, including the approved indication according to the SmPC
- Detailed description of the administration procedures for infusing HyQvia with a syringe driver pump and with a peristaltic infusion pump with counseling points to emphasize with the patient at each process step
 - Proper preparation and administration of HyQvia (i.e., infusion of the recombinant human hyaluronidase vial (HY) before the human normal immunoglobulin 10% vial (IG))
 - Following aseptic technique
 - Identification of early signs and symptoms of potential adverse events (e.g., local infusion site reactions, allergic-type hypersensitivity reactions) and measures to be taken in case reactions occur, including when to contact the HCP
- Patients and/or their caregivers will be asked to demonstrate to the HCP trainer that they can successfully administer HyQvia. Proper technique should be reviewed at regular intervals.
- The importance of reporting adverse reactions such as infusion-related reactions and allergic-type hypersensitivity reactions

The patient information pack:

- Patient information leaflet
- A patient/carer guide
- A patient diary
- **Patient/carer guide:**

- A detailed, step-by-step description of the correct preparation and administration technique for infusing HyQvia
 - Detailed description for the self-administration, infusion of HyQvia with a syringe driver pump and with a peristaltic infusion pump
 - A description of the potential risks(s) associated with the use of HyQvia namely: local infusion site reactions and allergic-type hypersensitivity reactions (signs and symptoms)
 - Recommendations for managing possible adverse events associated with HyQvia treatment as well as when to contact the HCP
 - Importance of reporting adverse events along with instructions on how to report
 - Website feature allows for clickable animations to guide patients through administration sequence.
- **Patient diary:**
 - An infusion log will be provided to document the time, date, dose, infusion-site location, and any reactions the patient experiences
 - The infusion log will also include a description of precaution(s) needed to minimise the potential adverse events associated with the use of HyQvia
 - The infusion log will help facilitate regular monitoring of the patient's health status and facilitate discussions with the HCP

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (2.5 G, 5 G, 10 G, 20 G AND 30 G)

1. NAME OF THE MEDICINAL PRODUCT

HyQvia 100 mg/mL solution for infusion for subcutaneous use
human normal immunoglobulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human normal immunoglobulin vial: 100 mg/mL, at least 98% is IgG
Maximum immunoglobulin A (IgA) content: 140 micrograms/mL.

3. LIST OF EXCIPIENTS

Human normal immunoglobulin vial: Glycine, water for injections.

Recombinant human hyaluronidase vial: human hyaluronidase. Sodium chloride, sodium phosphate, human albumin, ethylenediaminetetraacetic acid disodium, calcium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion for subcutaneous use

1 vial human normal immunoglobulin
2.5 g/25 mL
5 g/50 mL
10 g/100 mL
20 g/200 mL
30 g/300 mL

1 vial recombinant human hyaluronidase
1.25 mL
2.5 mL
5 mL
10 mL
15 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.
Do not mix the two vials prior to administration.
Infuse first the recombinant human hyaluronidase.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna, Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/840/001 2.5 g/25 mL
EU/1/13/840/002 5 g/50 mL
EU/1/13/840/003 10 g/100 mL
EU/1/13/840/004 20 g/200 mL
EU/1/13/840/005 30 g/300 mL

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

HyQvia 100 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL HUMAN NORMAL IMMUNOGLOBULIN (5 G, 10 G, 20 G AND 30 G)

1. NAME OF THE MEDICINAL PRODUCT

HyQvia 100 mg/mL infusion for subcutaneous use
human normal immunoglobulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Immunoglobulin: 100 mg/mL, at least 98% is IgG
Maximum immunoglobulin A (IgA) content: 140 micrograms/m.

3. LIST OF EXCIPIENTS

Glycine, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Infusion for subcutaneous use.

1 vial

5 g/50 mL

10 g/100 mL

20 g/200 mL

30 g/300 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use only.

Infuse 2nd.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna, Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/840/002 5 g/50 mL
EU/1/13/840/003 10 g/100 mL
EU/1/13/840/004 20 g/200 mL
EU/1/13/840/005 30 g/300 mL

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL HUMAN NORMAL IMMUNOGLOBULIN (2.5 G)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

HyQvia 100 mg/mL infusion for subcutaneous use
human normal immunoglobulin
SC use only.

2. METHOD OF ADMINISTRATION

Infuse 2nd.

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 g/25 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL RECOMBINANT HUMAN HYALURONIDASE (2.5 ML, 5 ML, 10 ML, 15 ML)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Infusion for subcutaneous use for HyQvia
hyaluronidase
Subcutaneous use only.

2. METHOD OF ADMINISTRATION

Infuse 1st.

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mL
5 mL
10 mL
15 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL RECOMBINANT HUMAN HYALURONIDASE (1.25 ML)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Infusion for subcutaneous use for HyQvia
hyaluronidase
SC use only.

2. METHOD OF ADMINISTRATION

Infuse 1st.

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.25 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

HyQvia 100 mg/mL solution for infusion for subcutaneous use human normal immunoglobulin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What HyQvia is and what it is used for
2. What you need to know before you use HyQvia
3. How to use HyQvia
4. Possible side effects
5. How to store HyQvia
6. Contents of the pack and other information

1. What HyQvia is and what it is used for

What HyQvia is

HyQvia contains two solutions for infusion (drip) under the skin (subcutaneous or SC infusion). It is supplied as a package containing one vial of human normal immunoglobulin 10% (the active substance) and one vial of recombinant human hyaluronidase (a substance which helps the human normal immunoglobulin 10% reach your blood).

Human normal immunoglobulin 10% belongs to a class of medicines called “human normal immunoglobulins”. Immunoglobulins are also known as antibodies and are found in healthy people’s blood. Antibodies are part of the immune system (the body’s natural defences) and help your body to fight infections.

How HyQvia works

The vial of immunoglobulins has been prepared from the blood of healthy people. The medicine works in exactly the same way as the immunoglobulins naturally present in the blood. The recombinant human hyaluronidase is a protein that makes it easier for the immunoglobulins to be infused (dripped) under the skin and to reach your blood system.

What HyQvia is used for

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

HyQvia is prescribed as replacement therapy to patients who do not have sufficient antibodies, including the following groups:

- patients with an inborn inability or reduced ability to produce antibodies (primary immunodeficiencies).
- patients who experience severe or recurrent infections due to a weakened immune system resulting from other conditions or treatments

2. What you need to know before you use HyQvia

Do not inject or infuse HyQvia

- if you are allergic to immunoglobulins, hyaluronidase, recombinant hyaluronidase or any of the other ingredients of this medicine (listed in section 6, “Contents of the pack and other information”).
- if you have antibodies against immunoglobulin A (IgA) in your blood. This may occur if you have IgA deficiency. Since HyQvia contains trace amounts of IgA, you might have an allergic reaction.
- into a blood vessel (intravenously).

Warnings and precautions

The following warnings and precautions should be taken into consideration before you receive or use HyQvia. If you have any questions, talk to your doctor or nurse.

Pregnancy, breast-feeding and fertility

The data on the effects of long-term use of recombinant human hyaluronidase on pregnancy, breast-feeding and fertility are limited. HyQvia should only be used by pregnant and breast-feeding women after discussion with your physician.

Allergic reactions

You may be allergic to immunoglobulins without knowing it. Allergic reactions such as sudden fall in blood pressure or anaphylactic shock (a sharp fall in blood pressure with other symptoms such as swelling of the throat, breathing difficulties and skin rash) are rare but they can occasionally occur even if you have not previously had problems with similar treatments. You are at increased risk of allergic reactions if you have IgA deficiency with anti-IgA antibodies. Signs or symptoms of these rare allergic reactions include:

- feeling light-headed, dizzy or faint,
- skin rash and itchiness, swelling in the mouth or throat, difficulty breathing, wheezing,
- abnormal heart rate, chest pain, blueness of lips or fingers and toes,
- blurred vision.

Your doctor or nurse will first infuse HyQvia slowly, and carefully monitor you throughout the first infusions so that any allergic reaction can be detected and treated immediately.

- ▶ If you notice any of these signs during the infusion, tell your doctor or nurse immediately. He or she will decide whether to slow down the infusion rate or stop the infusion completely.

Infusion speed

It is very important to infuse the medicine at the correct speed. Your doctor or nurse will advise you on the appropriate infusion speed to use when you are infusing HyQvia at home (see section 3, “How to use HyQvia”).

Monitoring during infusion

Certain side effects may occur more frequently if:

- you are receiving HyQvia for the first time.
- you have received another immunoglobulin and have been switched to HyQvia.
- there has been a long interval (e.g., more than 2 or 3 infusion intervals) since you last received HyQvia.
 - ▶ In such cases, you will be closely monitored during your first infusion and for the first hour after your infusion has stopped.

In all other cases you should be monitored during the infusion and for at least 20 minutes after you receive HyQvia for the first few infusions.

Home treatment

Before you start home treatment you should assign a person as guardian. You and your guardian will be trained to detect early signs of side effects, especially allergic reactions. This guardian should help you keep an eye on potential side effects. During the infusion you must look out for first signs of side effects (for further details see section 4, “**Possible side effects**”).

- ▶ If you experience any side effects, you or your guardian must stop the infusion immediately and contact a doctor.
- ▶ If you experience a severe side effect, you or your guardian must seek emergency treatment immediately.

Spread of localised infections

Do not infuse HyQvia into or around an infected or red swollen area on your skin because it may cause the infection to spread.

No long-term (chronic) changes in the skin were observed in the clinical studies. Any long-term inflammation, lumps (nodules) or inflammation that occur at the infusion site and last more than a few days should be reported to your physician.

Effects on blood tests

HyQvia contains many different antibodies, some of which can affect blood tests (serological tests).

- ▶ Tell your doctor about your treatment with HyQvia before any blood test.

Information on the source material of HyQvia

The human normal immunoglobulin 10% of HyQvia and human serum albumin (an ingredient of the recombinant human hyaluronidase) are made from human plasma (the liquid part of blood). When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and
- the testing of each donation and pools of plasma for signs of viruses/infections.

Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are used, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken for the manufacture of HyQvia are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus and for the non-enveloped hepatitis A virus and parvovirus B19.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in HyQvia, are protective.

It is strongly recommended that every time you use HyQvia, the following data are recorded in your treatment diary:

- the date of administration,
- the batch number of the medicine, and
- the injected volume, flow rate, the number and location of infusion sites.

Children and adolescents

The same indications, dose and frequency of infusion as for adults apply for children and adolescents (0-18 years).

Other medicines and HyQvia

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Vaccinations

HyQvia may reduce the effect of some virus vaccines such as measles, rubella, mumps and chicken pox (live virus vaccines). Therefore, after receiving HyQvia, you may have to wait for up to 3 months before receiving certain vaccines. You may have to wait for up to 1 year after receiving HyQvia before you can receive your measles vaccine.

- ▶ Please tell your vaccinating doctor or nurse about your treatment with HyQvia.

Driving and using machines

Patients may experience side effects (for example dizziness or nausea) during treatment with HyQvia that might affect the ability to drive and use machines. If this happens, you should wait until the reactions have disappeared.

HyQvia contains sodium

This medicine contains 5.0 – 60.5 mg sodium (main component of cooking/table salt) in each recombinant human hyaluronidase vial of HyQvia. This is equivalent to 0.25 – 3% of the recommended maximum daily dietary intake of sodium for an adult. The IG 10% component is essentially sodium-free.

3. How to use HyQvia

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

HyQvia has to be infused under the skin (subcutaneous or SC administration).

Treatment with HyQvia will be started by your doctor or nurse, but you may be allowed to use the medicine at home once you have received the first few infusions under medical supervision and you (and/or your guardian) have been adequately trained. You and your doctor will decide if you can use HyQvia at home. Do not begin treatment with HyQvia at home until you have received complete instructions.

Dosing

Your doctor will calculate the correct dose for you based on your body weight, any previous treatment you may have received and your response to treatment. The recommended starting dose is one that supplies 400 to 800 mg of active substance per kg of bodyweight per month. In the beginning you will receive one quarter of this dose at 1-week intervals. This will be increased step-wise to larger doses at 3- to 4-week intervals with the next infusions. Sometimes your doctor may recommend that larger doses are split and given at two sites at once. Your doctor may also adjust your dose depending on your response to treatment.

Starting treatment

Your treatment will be started by a doctor or nurse experienced in treating patients with a weak immune system and in guiding patients for home treatment. You will be watched carefully throughout the infusion and for at least 1 hour after stopping the infusion to see how well you tolerate the medicine. In the beginning your doctor or nurse will use a slow infusion speed and gradually increase it during the first infusion and in the following infusions. Once the doctor or nurse has found the right dose and speed of infusion for you, you may be allowed to give the treatment to yourself at home.

Home treatment

You will be instructed in:

- Germ-free (aseptic) infusion techniques,
- The use of an infusion pump or syringe driver (if needed),
- Keeping a treatment diary, and
- Measures to be taken in case of severe side effects.

You must carefully follow your doctor's instructions regarding the dose, infusion speed and schedule for infusing HyQvia so that your treatment works for you.

| | 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 you have an infusion site leakage

Ask your doctor or pharmacist or nurse if another needle size would be more appropriate for you. Any change of needle size would have to be supervised by the treating physician.

If you use more HyQvia than you should




If you think that you used more HyQvia than you should, speak to your doctor as soon as possible.

If you forget to use HyQvia

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

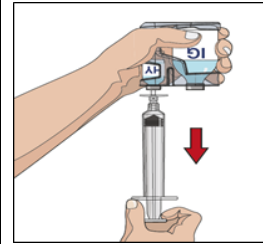
If you have any further questions on the use of this medicine, ask your doctor, or pharmacist or nurse.

Detailed Instructions for Use are provided in the section below.

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <p>1. Remove HyQvia from the box:</p> <ul style="list-style-type: none"> • Allow vials to reach room temperature. This may take up to 60 minutes. Do not use heating devices including microwave. • Do not heat up or shake HyQvia. • <i>Check each vial of HyQvia before using:</i> <ul style="list-style-type: none"> • Expiration date: Do not use beyond expiration date. • Colour: <ul style="list-style-type: none"> ○ The recombinant human hyaluronidase should be clear and colourless. ○ The human normal immunoglobulin 10% should be clear and colourless or pale yellow. ○ If either liquid is cloudy or has particles, do not use. • Cap: Purple protective cap is on the dual vial unit. Do not use the product if it does not have the cap. | |
| <p>2. Gather all supplies: Collect <i>all items</i> 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, pump, and treatment logbook and other supplies as needed.</p> |  |
| <p>3. Prepare a clean work area.</p> | |
| <p>4. Wash hands: Wash your hands thoroughly. Place all gathered supplies and open them as directed by your healthcare professional.</p> |  |
| <p>5. Open HyQvia dual vial unit(s):</p> <ul style="list-style-type: none"> • Remove 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. • Prepare to transfer the recombinant human hyaluronidase component of HyQvia by wiping each vial stopper with an alcohol swab, if directed and allow to air dry (at least 30 seconds). |  |

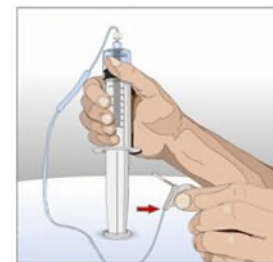
6. Prepare recombinant human hyaluronidase vial (HY):

- Remove the smaller sterile syringe from package and attach to a non-vented spike or needle (device).
- Pull back on the plunger, fill the smaller syringe with air equal to the amount of recombinant human hyaluronidase in the HY vial(s).
- Remove the cap of needle/non-vented transfer device.
- Insert the tip of the needle/non-vented transfer device into the 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 recombinant human hyaluronidase into the syringe.
- Repeat Step 6, if more than one vial of recombinant human hyaluronidase is needed for your dose.
- If possible, combine all of the recombinant human hyaluronidase needed for the entire dose of IgG into the same syringe.
- Point the syringe tip up and remove any air bubbles by pointing the syringe tip up and gently tapping the syringe with your finger. Slowly and carefully push the plunger to remove any remaining air.



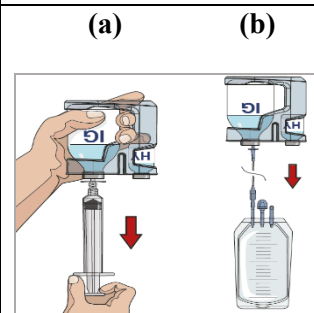
7. Prepare the needle set with the recombinant human hyaluronidase (HY):

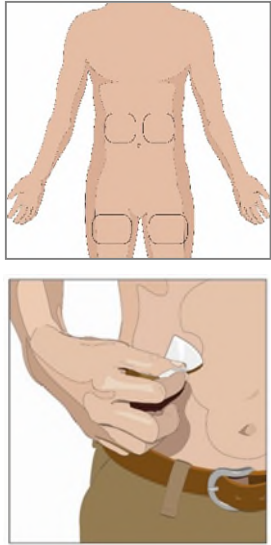
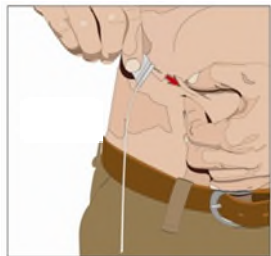
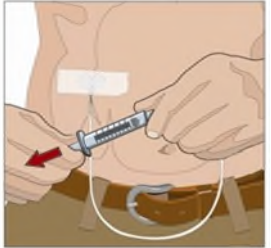
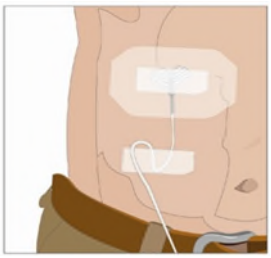
- Attach the syringe filled with recombinant human hyaluronidase to the needle set
- Push the plunger of smaller syringe to remove the air and fill the needle set up to the needle wings with the recombinant human hyaluronidase.
 - *Note:* Your healthcare professional may recommend using a “Y” connector (for more than one site) or other needle set configuration.

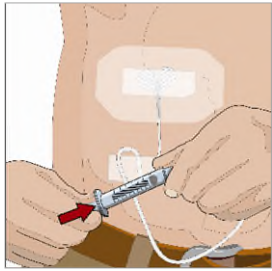
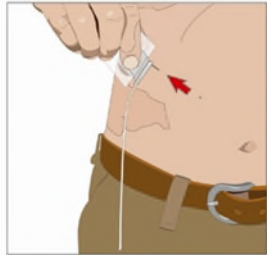


8. Prepare human normal immunoglobulin 10% vial:

- Prepare to transfer the immunoglobulin 10% component of HyQvia by wiping each vial stopper with an alcohol swab, if directed and allow to air dry (at least 30 seconds).
- The human normal immunoglobulin 10% of HyQvia may be infused either
 - by pooling from the vials either into larger syringe **(a)** or an infusion bag **(b)** as directed by your healthcare professional, depending upon the pump to be used; or
 - directly from the IG vial. Insert the spike of the vented pump tubing or spike and venting needle into human normal immunoglobulin 10% vial(s). Fill the administration pump tubing and set aside until the recombinant human hyaluronidase has been administered.
- If more than one vial is required for a full dose, spike subsequent vials after the first vial has been fully administered.



| | |
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| <p>9. Prepare the pump: Follow the manufacturer's instructions for preparing the pump.</p> | |
| <p>10. Prepare the infusion site:</p> <ul style="list-style-type: none"> • Choose an infusion site(s) in either the middle to upper abdomen or thigh. See image for infusion site locations. <ul style="list-style-type: none"> ○ Select sites on the opposite sides of the body if instructed to infuse in two sites for doses above 600 mL. • Avoid bony areas, visible blood vessels, scars and any areas of inflammation or infection. • Rotate infusion sites by choosing opposite sides of the body between future infusions. • If instructed by your health care professional, clean the infusion site(s) with an alcohol swab. Allow to dry (at least 30 seconds). |  |
| <p>11. Insert the needle:</p> <ul style="list-style-type: none"> • Remove the needle cover. Firmly grasp and pinch at least 2 to 2.5 cm of skin between two fingers. • Insert needle completely to the wings of the needle with a rapid motion straight into the skin at a 90-degree angle. Wings of needle should lay flat on the skin. • Secure needle in place with sterile tape. • Repeat this step if you have a second infusion site. | <p>90-degree angle to skin</p>  |
| <p>12. Check for proper needle placement before starting the infusion if instructed by your healthcare professional.</p> |  |
| <p>13. Secure the needle to the skin:</p> <ul style="list-style-type: none"> • 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. |  |

| | |
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| <p>14. Administer the recombinant human hyaluronidase infusion first:</p> <ul style="list-style-type: none"> • Slowly push the plunger of the smaller syringe with the recombinant human hyaluronidase at an initial rate per infusion site to approximately 1 to 2 mL per minute and increase as tolerated. • If using a pump, prepare the pump to infuse the recombinant human hyaluronidase at an initial rate per infusion site of 60 to 120 mL/hour and increase as tolerated. |  |
| <p>15. Administer the human normal immunoglobulin 10%: After infusing all of the content of the smaller syringe (recombinant human hyaluronidase), remove the syringe from the hub of the needle set. Attach the pump tubing or, the larger syringe containing human normal immunoglobulin 10% to the needle set. Administer the human normal immunoglobulin 10% with a pump at the rates prescribed by your healthcare professional and start the infusion.</p> | |
| <p>16. Flush the pump tubing when the infusion is complete if instructed by your healthcare professional:</p> <ul style="list-style-type: none"> • If instructed by your healthcare professional, attach a saline bag to the pump tubing/needle set to push the human normal immunoglobulin 10% up to the needle wings. | |
| <p>17. Remove needle set:</p> <ul style="list-style-type: none"> • Remove the needle set by loosening the dressing on all edges. • Pull the needle wings straight up and out. • Gently press a small piece of gauze over the needle site and cover with a protective dressing. • Throw away the needle(s) into the sharps container. <ul style="list-style-type: none"> ○ Dispose of the sharps container using instructions provided with the container, or contact your healthcare professional. |  |
| <p>18. Record the infusion:</p> <ul style="list-style-type: none"> • Remove the peel-off label from HyQvia vial, which has the product lot number and expiration date, and place the label in your treatment record/log book. • Write down the date, time, dose, site(s) of infusion (to assist in rotating sites) and any reactions after each infusion. • Throw away any unused product in the vial and the disposable supplies as recommended by your healthcare professional. • Follow up with physician as directed. | |

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everybody gets them. Certain side effects, such as headache, chills, or body aches, may be reduced by slowing the infusion rate.

Serious side effects

Infusions of medicines like HyQvia can occasionally result in serious, but rare, allergic reactions. You may experience a sudden fall in blood pressure and, in isolated cases, anaphylactic shock. Doctors are aware of these possible side effects and will monitor you during and after the initial infusions.

Typical signs or symptoms include: feeling light-headed, dizzy or faint, skin rash and itchiness, swelling in the mouth or throat, difficulty breathing, wheezing, abnormal heart rate, chest pain, blueness of lips or fingers and toes, blurred vision.

- Tell your doctor or nurse immediately if you notice any of these signs during the infusion.
- When using HyQvia at home, you must perform the infusion in the presence of an assigned guardian person who will help you watch out for allergic reactions, stop the infusion, and get help if necessary.
- Please also see section 2 of this leaflet about the risk of allergic reactions and using HyQvia at home.

Very common side effects (may affect more than 1 in 10 infusions):

Infusion site pain, including mild to moderate discomfort and tenderness. These reactions usually go away within a few days.

Common side effects (may affect up to 1 in 10 infusions):

Reactions at the infusion site: These include redness, swelling, itching, hardening, and rash at the site of infusion. These reactions usually go away within a few days. Headache, tiredness, nausea, vomiting, diarrhoea, abdominal pain, muscle or joint pain, chest pain, fever, feeling weak or unwell.

Uncommon side effects (may affect up to 1 in 100 infusions):

Chills, migraine, increased blood pressure, dizziness, abdominal bloating, skin rash/allergic rash/redness, itching, pain in chest, arms and/or legs, genital swelling (resulting from spread of swelling from the infusion site), swelling of the legs, feet and ankles, positive blood tests for antibodies.

Frequency not known (cannot be estimated from the available data):

Hypersensitivity, influenza-like illness, and infusion site leakage, inflammation of the layers lining the brain (aseptic meningitis).

Side effects seen with similar medicines

The following side effects have been observed with infusion of medicines like human normal immunoglobulin 10% given under the skin (subcutaneously). Although these side effects have so far not been seen with HyQvia, it is possible that someone using HyQvia may get them:

Trembling, oral tingling, fast heart beat, allergic reactions, flushing or pallor, coldness of hand or feet, shortness of breath, swelling of face, excessive sweating, muscle stiffness, change in liver function blood tests (alanine aminotransferase increased).

The following rare side effects have been observed in patients using medicines like human normal immunoglobulin 10% given into a vein (intravenously). These reactions have not been seen with HyQvia, but there is a small possibility that someone using HyQvia may get them:

Blood clots in blood vessels (thromboembolic reactions) leading to heart attack, stroke, blockage of deep veins, or of blood vessels supplying the lung (pulmonary embolism), kidney disorder or failure, destruction of red blood cells (haemolysis).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store HyQvia

Keep this medicine out of the sight and reach of children.

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

Store in a refrigerator (2°C to 8°C). Do not freeze.

Do not shake.

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

Do not use this medicine if the solutions are cloudy or have particles or deposits.

After opening, dispose of any unused solutions in the vials.

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

6. Contents of the pack and other information

What HyQvia contains

HyQvia is a dual vial unit containing:

- a solution of recombinant human hyaluronidase (Step 1 of HyQvia/Infuse first) and
- a solution of human normal immunoglobulin 10% (Step 2 of HyQvia/Infuse second).

The contents of each vial are described below:

1. Recombinant human hyaluronidase

This vial contains recombinant human hyaluronidase.

The other ingredients are sodium chloride, sodium phosphate, human albumin, ethylenediaminetetraacetic acid (EDTA) disodium, calcium chloride and water for injections (see also section 2, “**HyQvia contains sodium**”).

2. Human normal immunoglobulin 10%

One mL of the solution in this vial contains 100 mg of human normal immunoglobulin, of which at least 98% is immunoglobulin G (IgG).

The active substance of HyQvia is human normal immunoglobulin. This medicine contains trace amounts of immunoglobulin A (IgA) (not more than 140 micrograms/mL, 37 micrograms on average).

The other ingredients of this vial are glycine and water for injections.

What HyQvia looks like and contents of the pack

HyQvia is supplied as a pack containing:

- one glass vial of recombinant human hyaluronidase, and
- one glass vial of human normal immunoglobulin 10%.

The recombinant human hyaluronidase is a clear and colourless solution.
The human normal immunoglobulin 10% is a clear and colourless or pale yellow solution.

The following pack sizes are available:

| 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 |

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

Manufacturer:

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Takeda Belgium NV
Tel/Tél: +32 2 464 06 11
medinfoEMEA@takeda.com

Lietuva

Takeda, UAB
Tel: +370 521 09 070
medinfoEMEA@takeda.com

България

Такеда България ЕООД
Тел.: +359 2 958 27 36
medinfoEMEA@takeda.com

Luxembourg/Luxemburg

Takeda Belgium NV
Tel/Tél: +32 2 464 06 11
medinfoEMEA@takeda.com

Česká republika

Takeda Pharmaceuticals Czech Republic s.r.o.
Tel: +420 234 722 722
medinfoEMEA@takeda.com

Magyarország

Takeda Pharma Kft.
Tel: +36 1 270 7030
medinfoEMEA@takeda.com

Danmark

Takeda Pharma A/S
Tlf: +45 46 77 10 10
medinfoEMEA@takeda.com

Malta

Takeda HELLAS SA
Tel: +30 2106387800
medinfoEMEA@takeda.com

Deutschland

Takeda GmbH
Tel: +49 (0)800 825 3325
medinfoEMEA@takeda.com

Nederland

Takeda Nederland B.V.
Tel: +31 20 203 5492
medinfoEMEA@takeda.com

Eesti

Takeda Pharma AS

Norge

Takeda AS

Tel: +372 6177 669
medinfoEMEA@takeda.com

Ελλάδα

Takeda Ελλάς ΑΕ
Τηλ: +30 210 6387800
medinfoEMEA@takeda.com

España

Takeda Farmacéutica España S.A
Tel: +34 917 90 42 22
medinfoEMEA@takeda.com

France

Takeda France SAS
Tel. + 33 1 40 67 33 00
medinfoEMEA@takeda.com

Hrvatska

Takeda Pharmaceuticals Croatia d.o.o.
Tel: +385 1 377 88 96
medinfoEMEA@takeda.com

Ireland

Takeda Products Ireland Ltd
Tel: 1800 937 970
medinfoEMEA@takeda.com

Ísland

Vistor hf.
Sími: +354 535 7000
medinfoEMEA@takeda.com

Italia

Takeda Italia S.p.A.
Tel: +39 06 502601
medinfoEMEA@takeda.com

Κύπρος

Takeda Ελλάς ΑΕ
Τηλ.: +30 2106387800
medinfoEMEA@takeda.com

Latvija

Takeda Latvia SIA
Tel: +371 67840082
medinfoEMEA@takeda.com

Tlf: +47 800 800 30
medinfoEMEA@takeda.com

Österreich

Takeda Pharma Ges.m.b.H.
Tel: +43 (0) 800-20 80 50
medinfoEMEA@takeda.com

Polska

Takeda Pharma Sp. z o.o.
tel: +48223062447
medinfoEMEA@takeda.com

Portugal

Takeda Farmacêuticos Portugal, Lda.
Tel: + 351 21 120 1457
medinfoEMEA@takeda.com

România

Takeda Pharmaceuticals SRL
Tel: +40 21 335 03 91
medinfoEMEA@takeda.com

Slovenija

Takeda Pharmaceuticals farmacevtska družba d.o.o.
Tel: + 386 (0) 59 082 480
medinfoEMEA@takeda.com

Slovenská republika

Takeda Pharmaceuticals Slovakia s.r.o.
Tel: +421 (2) 20 602 600
medinfoEMEA@takeda.com

Suomi/Finland

Takeda Oy
Puh/Tel: 0800 774 051
medinfoEMEA@takeda.com

Sverige

Takeda Pharma AB
Tel: 020 795 079
medinfoEMEA@takeda.com

United Kingdom (Northern Ireland)

Takeda UK Ltd
Tel: +44 (0) 2830 640 902
medinfoEMEA@takeda.com

This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>