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 (IG 10%)**

One ml contains:

- Human normal immunoglobulin...................100 mg
- (purity of at least 98% immunoglobulin G (IgG))

Each vial of 25 ml contains: 2.5 g IgG
Each vial of 50 ml contains: 5 g IgG
Each vial of 100 ml contains: 10 g IgG
Each vial of 200 ml contains: 20 g IgG
Each vial of 300 ml contains: 30 g IgG

Distribution of the IgG subclasses (approx. values):

- IgG<sub>1</sub> ≥ 56.9%
- IgG<sub>2</sub> ≥ 26.6%
- IgG<sub>3</sub> ≥ 3.4%
- IgG<sub>4</sub> ≥ 1.7%

The maximum immunoglobulin A (IgA) content is 140 micrograms/ml.

Produced from the plasma of human donors.

Excipients with known effect:

**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 0.16 mmol (3.68 mg) per 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. Recombinant human hyaluronidase is a clear, colourless solution.
4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults (≥ 18 years) in primary immunodeficiency syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- IgG subclass deficiencies with recurrent infections.

Replacement therapy in adults (≥ 18 years) in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

4.2 Posology and method of administration

Treatment should be commenced and initially monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

HyQvia is comprised of two vials. 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.

<table>
<thead>
<tr>
<th>Recombinant human hyaluronidase</th>
<th>Human normal immunoglobulin 10%</th>
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<tbody>
<tr>
<td>Volume (ml)</td>
<td>Grams Protein</td>
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<td>1.25</td>
<td>2.5</td>
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<td>2.5</td>
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<td>15</td>
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Posology
The dose level may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimen is given as a guideline.

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/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 monthly
dose of HyQvia is the same as for subcutaneous treatment, but adjusted to 3- or 4-weeks interval.

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

Paediatric population
The long-term safety and potential risk on fertility of HyQvia in children and adolescents
aged 0 to 18 years has not been established. 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.

In case facilitated subcutaneous infusion of HyQvia is used for home treatment, therapy should be
initiated 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, if needed, the keeping
of a treatment diary, and measures to be taken in case of adverse reactions.

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.

The HyQvia components may be infused using a variable rate, electromechanical pump with
a subcutaneous needle set that is at least 24 gauge and an administration set that is compatible
with the pump.

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.

The suggested site(s) for the infusion of the medicinal product are the abdomen and thighs. If two sites
are used, the two infusion sites should be on contra lateral sides of the body. Avoid bony prominences.

First, the full dose of recombinant human hyaluronidase solution is infused at a rate of 1 to 2 ml/minute
per infusion site. Within 10 minutes of completing the infusion of recombinant human hyaluronidase,
the infusion of the required dose of IG 10% has to be initiated at the same needle site. If two infusion
sites are used, the total dosages of the recombinant human hyaluronidase and IG 10% each have to be
divided before start of the infusion.

The following infusion rates of the IG 10% are recommended:

- Patients with a body weight of 40 kg or above: IG 10% should be infused at an initial rate
  of 10 ml/hour/infusion site. If well tolerated, the rate of the administration may be increased
  at intervals of at least 10 minutes to a maximum of 240 ml/hour/site for the initial one or two
  infusions. For subsequent infusions the rate can be adjusted to a maximum of 300 ml/hour/site.
- Patients with a body weight under 40 kg: IG 10% should be infused at an initial rate
  of 5 ml/hour/infusion site. If well tolerated, the rate of the administration may be increased at
  intervals of at least 10 minutes to a maximum of 80 ml/hour/site for the initial one or two
  infusions. For subsequent infusions the rate can be adjusted to a maximum of 160 ml/hour/site.

For instructions on how to use the medicinal product, see section 6.6.
4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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

Systemic hypersensitivity to hyaluronidase or recombinant human hyaluronidase.

HyQvia must not be given intravenously.

4.4 Special warnings and precautions for use

HyQvia should not be used by women who are pregnant or are planning to become pregnant
(see section 4.6).

The recommended infusion rate given in section 4.2 should be adhered to. Patients should be
closely monitored and carefully observed for any adverse reactions 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 treatment has been stopped for a prolonged period.

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 very rare cases
of IgA deficiency with anti-IgA antibodies and these patients should be treated with
caution. The IG 10% component of the medicinal product contains trace amounts of
IgA (maximum content is 140 micrograms/ml).

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.

Potential complications can often be avoided by ensuring that:

- Patients are not sensitive to human normal immunoglobulin, by first injecting the product
  slowly (see section 4.2).
- Patients are carefully monitored for any symptoms throughout the infusion period. In particular,
  patients naive to human normal immunoglobulin, patients switched from an alternate 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, standard medical treatment for shock should be implemented.

**Hypersensitivity to 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.

**Spread of localized infections**

The medicinal product should not be injected at or around an infected or acutely inflamed area because of the danger of spreading a localized infection.

**Reactions reported to occur with intravenously administered immunoglobulins**

Thromboembolic events (e.g. myocardial infarction, cerebral vascular accident, deep vein thrombosis, and pulmonary embolism), renal dysfunction/failure, aseptic meningitis syndrome, and hemolysis have been observed with IG 10% administered intravenously and cannot be excluded with use of HyQvia.

Thrombotic events and haemolysis have also been reported in association with the subcutaneous administration of immunoglobulin products.

**Thrombotic events**

- If a patient has known risk factors, or is part of a risk group 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 immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity), these should be noted in the patient records. Baseline assessment of all risk factors including viscosity should be considered for patients at risk.
- 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.
- Patients should be sufficiently hydrated before use of immunoglobulins.

**Haemolytic anaemia**

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

**Acute renal failure**

Cases of acute renal failure have been reported in patients receiving intravenous immunoglobulin therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

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

**Aseptic meningitis syndrome (AMS)**

Aseptic meningitis syndrome has been reported to occur in association with intravenous immunoglobulin treatment. Discontinuation of intravenous immunoglobulin treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following intravenous immunoglobulin treatment. 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.

**Information about some of the ingredients**

HyQvia does not contain sugars. The IG 10% component contains trace amounts of sodium. Recombinant human hyaluronidase contains 0.16 mmol (3.68 mg) sodium per ml, with a maximum daily dose of approximately 120 mg. This may have to be taken into consideration for patients on a controlled sodium diet.

**Interference with serological testing**

After injection 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 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).

**Information on safety with respect to 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.

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

**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 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.

4.6 Fertility, pregnancy and lactation

**Pregnancy**

No clinical studies have been conducted with HyQvia in pregnant women. HyQvia should not be used by women who are pregnant or are planning to become pregnant and an alternate treatment should be considered. It is recommended that women of childbearing potential take appropriate measures to prevent pregnancy during HyQvia treatment. If a woman becomes pregnant, treatment with HyQvia should be stopped. In addition, the treating physician should encourage her of the possibility of participating in the pregnancy registry.

**Breast-feeding**

There are no safety data on the use of HyQvia in breast-feeding women available. HyQvia should not be used during breast-feeding.

**Fertility**

Clinical experience with immunoglobulins suggests that no harmful effects of IG 10% on fertility are to be expected. With HyQvia there are currently no clinical safety data on development of the reproductive system available.

Male and female patients of reproductive potential should be advised that there are insufficient long-term data on the use of HyQvia. Its effect on human fertility and the potential for adverse effects on conception is currently unknown. These patients should be provided with the HyQvia Patient Education Materials for further information.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity 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. Patients who experience adverse reactions (such as dizziness and nausea) during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

**Summary of the safety profile**

The most frequently reported adverse reactions (ARs) of HyQvia occurring at a rate of 0.203 per infusion 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.

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 gammaglobulin products.
Local reactions at infusion site: swelling, soreness, redness, induration, local heat, local pain, itching, bruising and rash.

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

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

For information on viral safety see section 4.4.

**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 injection 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 and tolerability of HyQvia was evaluated in a phase 3 study in 83 patients with PID (including 21 between 2 and 16 years) receiving infusions at 3- to 4-weeks interval.

The ARs are summarized and categorised according to the MedDRA System Organ Classification and frequency in the table below.
Frequency per infusion has been evaluated using the following criteria: 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).

<table>
<thead>
<tr>
<th>System Organ Class, MedDRA</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
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<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>Nausea</td>
<td>Abdominal pain upper</td>
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<td></td>
<td>Diarrhoea</td>
<td>Oral pain</td>
<td></td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Local reactions (Total)</td>
<td>Local reactions:</td>
<td>Local reactions:</td>
<td></td>
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<tr>
<td></td>
<td>Discomfort/Pain</td>
<td>• Erythema</td>
<td>• Infusion site mass</td>
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<td></td>
<td></td>
<td>• Swelling/Oedema</td>
<td>• Nodule</td>
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<td></td>
<td></td>
<td>• Pruritus</td>
<td>• Infusion site:</td>
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<td></td>
<td></td>
<td>Fatigue</td>
<td>• warmth</td>
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<td>• hematoma</td>
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<td>• haemorrhage</td>
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<td></td>
<td>Pyrexia</td>
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<td></td>
<td>Oedema peripheral</td>
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<td></td>
<td></td>
<td></td>
<td>Chills</td>
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<td></td>
<td>Malaise</td>
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<td>Asthenia</td>
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<td></td>
<td>Feeling abnormal</td>
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<td></td>
<td>Gravitational oedema</td>
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<tr>
<td>Investigations</td>
<td>Antibody test positive</td>
<td>Coombs test positive</td>
<td>♦ Decreased appetite</td>
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<td></td>
<td></td>
<td>Lymphocyte count decreased</td>
<td>White blood cell count</td>
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<td>decreased</td>
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<td>Weight decreased</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Decreased appetite</td>
<td>♦ Myalgia</td>
<td>♦ Arthralgia</td>
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<tr>
<td></td>
<td></td>
<td>♦ Groin pain</td>
<td>♦ Pain in extremity</td>
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<td></td>
<td></td>
<td>♦ Musculoskeletal chest pain</td>
<td>♦ Decreased appetite</td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Migraine</td>
<td>Dizziness</td>
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<td></td>
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<td>Burning sensation</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Vulvovaginal pruritus</td>
<td>Genital Oedema</td>
<td>♦ Nasal congestion</td>
<td></td>
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<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>♦ Decreased appetite</td>
<td>♦ Migraine</td>
<td>♦ Dizziness</td>
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<td></td>
<td></td>
<td></td>
<td>♦ Burning sensation</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Erythema</td>
<td>Maculo-papular rash</td>
<td>♦ Hypertension</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>Blood pressure decreased</td>
<td>♦ Decreased appetite</td>
<td></td>
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</tbody>
</table>
Description of selected adverse reactions
Local reactions observed during the 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
HyQvia was evaluated in 21 paediatric patients between 4 and 16 years old (13 were 4 to < 12 years and 8 were 12 to < 16 years old). Results of the studies indicated similar safety profiles in adults and paediatric patients, such as nature, frequency or seriousness or reversibility of adverse reactions.

4.9 Overdose
Consequences of an overdose of HyQvia are not known. When immunoglobulins are administered intravenously, overdose may lead to fluid overload and hyperviscosity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group (human normal immunoglobulin): immune sera and immunoglobulins: immunoglobulins, normal human, ATC code: J06BA

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 modifies the permeability of connective tissue through the hydrolysis of hyaluronan. Hyaluronan is a polysaccharide found in the intercellular ground substance of connective tissue and of certain specialized tissues. It is degraded by naturally occurring hyaluronidase and has a very fast turnover in subcutaneous tissue. As a permeation enhancer, recombinant human hyaluronidase accelerates the break-down of hyaluronan, resulting in a temporary increase in the permeability of the interstitial matrix that facilitates more rapid dispersion and absorption and improved bioavailability of the IG 10%.

The naturally occurring rapid regeneration of hyaluronan results in complete restoration of the interstitial barrier within 24 to 48 hours.

Clinical efficacy and safety
Efficacy and safety of HyQvia was assessed in a phase 3 study 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/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).

Paediatric population

HyQvia was evaluated in 21 paediatric patients, including 13 patients between 4 and < 12 years and 8 between 12 and < 16 years, who were treated for more than one year (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. However, these data are not sufficient to establish the safety and efficacy of HyQvia in this age group. See sections 4.2 and 4.8.

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

With administration of HyQvia, peak serum IgG levels are achieved in the recipient’s circulation after a delay of approximately 3 to 5 days.

Data from the clinical trial 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 the phase 3 efficacy and safety study in 60 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.

| 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; 17.1)       | 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 98.4)    | 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) |

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

Non-clinical data for the IG 10% component of HyQvia 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. In vitro genotoxicity studies did not reveal mutagenicity. Since clinical experience provides no evidence for carcinogenic potential of immunoglobulins, no experimental studies in heterogeneous species were performed.

Hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and developmental toxicity. Reversible effects on fertility have been reported in male and female guinea pigs immunized to produce antibodies to hyaluronidase. However, antibodies to hyaluronidase did not influence reproduction in mouse, rabbit, sheep, or cynomolgus monkey.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

2 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.

IG 10% is a clear or slightly opalescent and colourless or pale yellow solution. Recombinant human hyaluronidase is a clear, colourless solution. Do not use solutions that are cloudy or have deposits.

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

7. MARKETING AUTHORISATION HOLDER

Baxter Innovations GmbH
Industriestrasse 67
A-1221-Vienna, Austria

8. MARKETING AUTHORISATION NUMBER(S)
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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)
Baxter Healthcare Corporation
4501 Colorado Boulevard
Los Angeles, California
USA
Manufacture of intermediate Precipitate G from human plasma.

Baxter AG
Industriestrasse 131
1221-Vienna
Austria
Manufacture of intermediate Precipitate G from human plasma.

Baxter Manufacturing S.p.A.
Via della Chimica 5
02010 Santa Rufina, Cittaducale, Rieti
Italy
Manufacture of intermediate Precipitate G from human plasma.

Baxter S.A.
Boulevard René Branquart, 80
B-7860 Lessines
Belgium
Manufacture of Ultrafiltrate Centrifugate of Immune Globulin 10% from Precipitate G.

Name and address of the manufacturer responsible for batch release
Baxter S.A.
Boulevard René Branquart, 80
B-7860 Lessines
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in
the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

Prior to launch in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe HyQvia are provided with an Educational pack.

The educational pack should contain the following:
1. Summary of Product Characteristics and Patient Information Leaflets
2. Patient information cards
3. Text statement for the doctor to be mentioned on the educational pack:
   - A patient information leaflet and a patient information card should be given to the patient before treatment with HyQvia is initiated.
   - Should any woman become pregnant whilst on treatment with HyQvia, HyQvia should be discontinued and treatment switched to an alternative IgG treatment which does not contain recombinant hyaluronidase. In addition, the patients should be encouraged to participate in the pregnancy registry.
   - Information on the availability of a pregnancy registry and on how to enrol patients in it.

The Patient information card should include information on the following key elements:

Information on antibodies against recombinant hyaluronidase

- HyQvia contains recombinant human hyaluronidase that facilitates the dispersion and absorption of Immunoglobulin G and some patients receiving HyQvia may develop antibodies against it.
- In clinical trials up to 18% of patients receiving HyQvia developed antibodies against recombinant human hyaluronidase.
- These antibodies may potentially react against the hyaluronidase that is naturally present in most tissue of the human body but it is unknown if it has any clinical consequences.
• In clinical trials no adverse reactions were observed that were considered related to the presence of antibodies against recombinant human hyaluronidase but the duration of treatment was limited up to 36 months and the potential for long term effects is unknown.
• Their effect on human fertility and the potential for adverse effects on conception is unknown.

Information on fertility

• Reversible contraceptive effects have been reported in male and female guinea pigs immunised to produce antibodies to hyaluronidase. However, antibodies to hyaluronidase did not influence reproduction in mouse, rabbit, sheep, or cynomolgus monkey.
• The effect of antibodies against recombinant hyaluronidase on male or female human fertility is unknown.

Information on pregnancy:

• Antibodies against recombinant human hyaluronidase may cross the placenta.
• Animal studies reveal no special hazard for humans based on conventional studies of developmental toxicity.
• No clinical studies have been conducted with HyQvia in pregnant women. The potential impact of antibodies against recombinant hyaluronidase on human embryo or foetal development is currently unknown.
• HyQvia should not be used by women who are pregnant or are planning to become pregnant. An alternative treatment that does not contain recombinant hyaluronidase should be considered.
• In the event a woman nevertheless becomes pregnant while being treated with HyQvia, treatment with HyQvia should be stopped and an alternate IgG treatment that does not contain recombinant hyaluronidase should be discussed with the treating doctor.
• It is recommended that women of childbearing potential take appropriate measures to prevent pregnancy during HyQvia treatment.
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)**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HyQvia 100 mg/ml solution for infusion for subcutaneous use</td>
</tr>
<tr>
<td>Human normal immunoglobulin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human normal immunoglobulin vial: 100 mg/ml, at least 98% is IgG</td>
</tr>
<tr>
<td>Maximum immunoglobulin A (IgA) content: 140 micrograms/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human normal immunoglobulin vial: Glycine, water for injections.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for infusion for subcutaneous use</td>
</tr>
<tr>
<td>1 vial human normal immunoglobulin</td>
</tr>
<tr>
<td>2.5 g / 25 ml</td>
</tr>
<tr>
<td>5 g / 50 ml</td>
</tr>
<tr>
<td>10 g / 100 ml</td>
</tr>
<tr>
<td>20 g / 200 ml</td>
</tr>
<tr>
<td>30 g / 300 ml</td>
</tr>
<tr>
<td>1 vial recombinant human hyaluronidase</td>
</tr>
<tr>
<td>1.25 ml</td>
</tr>
<tr>
<td>2.5 ml</td>
</tr>
<tr>
<td>5 ml</td>
</tr>
<tr>
<td>10 ml</td>
</tr>
<tr>
<td>15 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For subcutaneous use only.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>
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

Baxter Innovations GmbH
A-1221 Vienna, Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000/001 2.5 g/25 ml
EU/0/00/000/000/002 5 g/50 ml
EU/0/00/000/000/003 10 g/100 ml
EU/0/00/000/000/004 20 g/200 ml
EU/0/00/000/000/005 30 g/300 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.
15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

HyQvia 100 mg/ml
**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

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

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HyQvia 100 mg/ml infusion for subcutaneous use</td>
</tr>
<tr>
<td>Human normal immunoglobulin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin: 100 mg/ml, at least 98% is IgG</td>
</tr>
<tr>
<td>Maximum immunoglobulin A (IgA) content: 140 micrograms/ml.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine, water for injections.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion for subcutaneous use.</td>
</tr>
<tr>
<td>1 vial</td>
</tr>
<tr>
<td>5 g / 50 ml</td>
</tr>
<tr>
<td>10 g / 100 ml</td>
</tr>
<tr>
<td>20 g / 200 ml</td>
</tr>
<tr>
<td>30 g / 300 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous use only.</td>
</tr>
<tr>
<td>Infuse 2nd.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

| 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 |

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
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

Baxter Innovations GmbH
A-1221 Vienna, Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000/002 5 g/50 ml
EU/0/00/000/000/003 10 g/100 ml
EU/0/00/000/000/004 20 g/200 ml
EU/0/00/000/000/005 30 g/300 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
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
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIAL LABEL RECOMBINANT HUMAN HYALURONIDASE (2.5 ML, 5 ML, 10 ML, 15 ML)</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>2.5 ml</th>
<th>5 ml</th>
<th>10 ml</th>
<th>15 ml</th>
</tr>
</thead>
</table>

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.

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 to

- adult patients aged 18 years and over with an inability or reduced ability to produce antibodies (primary immunodeficiencies), which includes conditions such as:
  - low immunoglobulin levels (hypogammaglobulinaemia) or absence of immunoglobulins (agammaglobulinaemia) in the blood;
  - a combination of low immunoglobulin levels, frequent infections, inability to produce adequate amounts of antibodies after vaccination, and other symptoms such as immune reactions against your own body or cancer (common variable immunodeficiency);
  - a combination of low levels or absence of immunoglobulins and absent or non-working T-cells (a kind of white blood cells also part of the immune system) in the blood (severe combined immunodeficiency);
  - lack of certain kinds of immunoglobulins (IgG subclasses) which results in frequent infections.

- adult patients aged 18 years and over with certain kinds of blood cancer (such as chronic lymphocytic leukaemia or myeloma) which lead to very low antibody levels in the blood (hypogammaglobulinaemia) and frequent bacterial infections.

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.

Children and adolescents

Do not give this medicine to children and adolescents aged 0-18 years because its safety with long-term use is not known.

Pregnancy, breast-feeding and fertility

The effects of long-term use of recombinant human hyaluronidase on male and female fertility are currently not known. Prior to treatment with HyQvia, ask your doctor for further information on the potential effect of HyQvia on fertility and pregnancy.

HyQvia should not be used by pregnant and breast-feeding women. It is recommended that women of childbearing age take appropriate measures to prevent pregnancy during treatment with HyQvia. If you become pregnant, are breast-feeding, or think you may be pregnant or are planning to have a baby, treatment with HyQvia should be stopped and you should discuss alternative treatment options with your doctor. In addition, if you become pregnant when using HyQvia, you should discuss with your doctor the possibility of participating in a pregnancy registry in order to collect data on your pregnancy and the development of the baby. The purpose of such registry is to collect and share data only with the public health authorities responsible for monitoring the safety of this product. Participation in the registry is voluntary.
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 injection sites.

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
The recombinant human hyaluronidase of HyQvia contains small amounts (3.68 mg per ml) of sodium. This may have to be considered for patients who are on a controlled sodium diet.
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.

- For patients with a bodyweight of 40 kg or more, the initial rate is 10 ml per hour per infusion site. If well tolerated, this may be increased at intervals of at least 10 minutes to 240 ml per hour per site for the initial two infusions. For subsequent infusions the rate may be increased to 300 ml per hour per infusion site;
- For patients with a bodyweight under 40 kg, the initial rate is 5 ml per hour per infusion site. If well tolerated this may be increased at intervals of at least 10 minutes to 80 ml per hour per site for the initial two infusions. For all subsequent infusions the rate may be increased to 160 ml per hour per infusion site.

**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.

<table>
<thead>
<tr>
<th><strong>1. Remove HyQvia from the box:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allow vials to reach room temperature. This may take up to 60 minutes.</td>
</tr>
<tr>
<td>• <strong>Do not heat up or shake HyQvia.</strong></td>
</tr>
<tr>
<td>• <strong>Check each vial of HyQvia before using:</strong></td>
</tr>
<tr>
<td>• <strong>Expiration date:</strong> Do not use beyond expiration date.</td>
</tr>
<tr>
<td>• <strong>Colour:</strong></td>
</tr>
<tr>
<td>• The recombinant human hyaluronidase should be clear and colourless.</td>
</tr>
<tr>
<td>• The human normal immunoglobulin 10% should be clear and colourless or pale yellow.</td>
</tr>
<tr>
<td>• If either liquid is cloudy or has particles, do not use.</td>
</tr>
<tr>
<td>• <strong>Cap:</strong> Protective cap is on the dual vial unit. Do not use the product if it does not have the cap.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. Gather all supplies:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect all items for your infusion. Items include: dual vial unit(s) of HyQvia, infusion supplies (subcutaneous needle set, solution container (bag or syringe), sterile clear bandage and tape, pump tubing, needles or vial access devices, syringes, gauze and tape), sharps container, variable rate electromechanical infusion pump, and treatment logbook and other supplies as needed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. Prepare a clean work area.</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>4. Wash hands:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wash your hands thoroughly. Place all gathered supplies and open them as directed by your healthcare professional.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. Open HyQvia dual vial unit(s):</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Remove blue protective caps to expose the vial stoppers.</td>
</tr>
</tbody>
</table>
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.
- Remove the cap of device, insert the tip of device into the center of the vial stopper and push straight downward. Push the air into the vial.
- Turn the vial upside down, with the device remaining in the vial. The device 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 human normal immunoglobulin 10% vial:**
- The human normal immunoglobulin 10% of HyQvia may be infused either
  - by pooling from the vials either into an infusion bag or the larger syringe as directed by your healthcare professional, depending upon the variable rate electromechanical infusion pump to be used; or
  - directly from the IG vial. Insert vented spike 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.

8. **Prepare the needle set with the recombinant human hyaluronidase:**
- 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 pump tubing configuration.

9. **Program the variable rate electromechanical pump:**
- Follow the manufacturer’s instructions for preparing the variable rate electromechanical pump.
- Program the infusion rates of the human normal immunoglobulin 10% as instructed by your healthcare professional.
10. **Prepare the infusion site:**
- Choose an infusion site(s) in either the abdomen or thigh. See image for infusion site locations.
  - 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).

11. **Insert the needle:**
- Remove the needle cover. Firmly grasp and pinch at least one inch 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.

12. **Check for proper needle placement before starting the infusion if instructed by your healthcare professional.**

13. **Secure the needle to the skin:**
- Secure the needle(s) in place by putting a sterile clear bandage over the needle.
- Check infusion site(s) occasionally throughout the infusion for dislodgement or leaking.

14. **Start the recombinant human hyaluronidase infusion first:**
- Slowly push the plunger of the smaller syringe with the recombinant human hyaluronidase at an initial rate per infusion site to approximately 1 to 2 ml per minute and increase as tolerated.
- If using a pump, program the pump to infuse the recombinant human hyaluronidase at an initial rate per infusion site of 1 to 2 ml per minute and increase as tolerated.
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 or pump.
   
   Attach the vial, the larger syringe or infusion bag containing human normal immunoglobulin 10% to the variable rate electromechanical infusion pump tubing.
   
   Administer the human normal immunoglobulin 10% at the rates prescribed by your healthcare professional.

16. **Flush the pump tubing when the infusion is complete if instructed by your healthcare professional:**
   - If instructed by your healthcare professional, attach a saline bag/flush syringe to the pump tubing/needle set to push the human normal immunoglobulin 10% up to the needle wings.

17. **Remove needle set:**
   - Remove the needle set by loosening the dressing on all edges.
   - Pull the needle wings straight up and out.
   - Gently press a small piece of gauze over the needle site and cover with a protective dressing.
   - Throw away the needle(s) into the sharps container.
     - Dispose of the sharps container using instructions provided with the container, or contact your healthcare professional.

18. **Record the infusion:**
   - Remove the peel-off label from HyQvia vial, which has the product lot number and expiration date, and place the label in your treatment record/log book.
   - Write down the date, time, dose, site(s) of infusion (to assist in rotating sites) and any reactions after each infusion.
   - Throw away any unused product in the vial and the disposable supplies as recommended by your healthcare professional.
   - Follow up with physician as directed.

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.

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Very common and common side effects
The most common side effects of HyQvia (affecting more than 1 in 10 infusions) are:
- Reactions at the infusion site. These include mild to moderate pain/discomfort, redness, swelling, itching, hardening, warmth, bruising, and rash at the site of infusion. These reactions usually go away within a few days.

Other side effects
The following side effects are common (affects up to 1 in 100 infusions):
- headache
- tiredness

The following side effects are uncommon (affects up to 1 in 1,000 infusions):
- fever, chills
- migraine
- increased or decreased blood pressure
- dizziness
- nausea, vomiting, diarrhoea, abdominal pain
- decreased appetite, weight loss
- feeling weak, unwell or abnormal
- skin rash/redness
- burning sensation
- nasal congestion
- pain in mouth
- muscle or joint pain
- pain in chest, groin, arms and/or legs
- vaginal itching
- genital swelling (resulting from spread of swelling from the infusion site)
- swelling of the legs, feet and ankles
- positive blood tests for antibodies
- decreased white blood cell count

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.
- Tingling, trembling, oral tingling
- Fast heart beat
- Flushing or pallor, coldness of hand or feet
- Shortness of breath
- Swelling of face
- Excessive sweating, itching
- Back pain, 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
- Inflammation of the layers lining the brain (aseptic meningitis)
- Destruction of red blood cells (haemolysis).
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

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 they 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:

<table>
<thead>
<tr>
<th>Recombinant human hyaluronidase</th>
<th>Human normal immunoglobulin 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td>Grams</td>
</tr>
<tr>
<td>1.25</td>
<td>2.5</td>
</tr>
<tr>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Baxter Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

Manufacturer:
Baxter, S.A.
Boulevard René Branquart
B-7860 Lessines
Belgium

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

**België/Belgique/Belgien**
Baxter Belgium SPRL
Tél./Tel.: +32-2-386 80 00

**България**
Бакстер България ЕООД
tel.: + 359 2 9808482

**Česká republika**
BAXTER CZECH spol.s r.o.
Tel. +420 225774111

**Danmark**
Baxter A/S
Tlf.: +454816 64 00

**Luxembourg/Luxemburg**
Baxter Belgium SPRL
Tél./Tel.: +32-2-386 80 00

**Magyarország**
Baxter Hungary Kft
Tel.: +36 1 202 1980

**Malta**
Baxter Healthcare Ltd
Tel.: +44 1635 206345

**Nederland**
Baxter B.V.
Tel.: +31-30-2488911
Deutschland
Baxter Deutschland GmbH
Tel.: +49 89 31701 0

Eesti
OÜ Baxter Estonia
Tel.: +372 6 515 120

Ελλάδα
Baxter Hellas EΠΕ
Τηλ.: +30-210-28 80 000

España
Baxter S.L.
Tel.: +34-96-2722800

France
Baxter S.A.S.
Tél.: +33-1-3461-5050

Irland
Baxter Healthcare Ltd
Tel.: +353-1-2065500

Ísland
Icepharma hf.
Sími: +354-540-8000

Italia
Baxter S.p.A.
Tel.: +39-06 32491-1

Κύπρος
Baxter Hellas ΕΠΕ
Τηλ.: +30-210-28 80 000

Latvija
SIA Baxter Latvia
Tel.: +371 67784784

Lietuva
UAB Baxter Lithuania
Tel.: +370 5 269 16 90

Norge
Baxter AS
Tlf.: +47-22 58 48 00

Österreich
Baxter Healthcare GmbH
Tel.: +43 (0)1 71120-0

Polska
Baxter Polska Sp. z o.o.
Tel.: +48 22 4883 777

Portugal
Baxter Médico Farmacêutica Lda
Tel.: +351 21-925 25 00

România
Farmaceutica REMEDIA SA
Tel.: + 40-21-321 16 40

Slovenija
Baxter d.o.o.
Tel.: +386 1 420 16 80

Slovenská republika
Baxter Slovakia, s.r.o.
Tel.: +421 2 59418455

Suomi/Finland
Baxter Oy
Puh/Tel.: +358-9-862-1111

Sverige
Baxter Medical AB
Tel.: +46-8-632 64 00

United Kingdom
Baxter Healthcare Ltd
Tel.: +44 1635 206345

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: