Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

HyQvia®

Solution for subcutaneous infusion

Active ingredient and its quantity:
100 mg/ml Human normal immunoglobulin

Inactive ingredients and allergens in the medicine: see section 2 'Important information about some of this medicine's ingredients' and section 6.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. What is this medicine intended for?

HyQvia is prescribed as replacement therapy to adults, children and adolescents (aged 0-18 years) with:

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

Therapeutic group: serum containing antibodies and immunoglobulins. Human normal immunoglobulin 10% belongs to the group of medicines called "human normal immunoglobulins".

Immunoglobulins are also called "antibodies" and are present in healthy people's blood. Antibodies are part of the immune system (the body's natural defense system) and help your body to fight infections.

What HyQvia is
HyQvia pack contains two vials of solutions for subcutaneous infusion:
one vial of human normal immunoglobulin 10% (the active ingredient) and one vial of recombinant human hyaluronidase (a substance which helps the human normal immunoglobulin 10% reach your blood).

How HyQvia works
The vial of immunoglobulins is 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 the blood system.

2. Before using this medicine

Do not use this medicine:

- If you are sensitive (allergic) to the active ingredient - immunoglobulins, to hyaluronidase, recombinant hyaluronidase or to any of the other ingredients contained in this medicine (see the list of inactive ingredients in section 6).
- 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 may develop an allergic reaction.

- Do not administer into a vein (IV) or into a muscle (IM).

Special warnings about using this medicine

Allergic reactions
You may be allergic to immunoglobulins without knowing it. Allergic reactions, such as a sudden drop in blood pressure or anaphylactic shock (a sharp drop in blood pressure accompanied by other symptoms, such as swelling of the throat, breathing difficulties and skin rash) are rare, but they may occasionally occur even if you have not previously had problems with similar treatments. You are at increased risk of developing allergic reactions if you have IgA deficiency with anti-IgA antibodies. Signs and symptoms of these rare allergic reactions include:
- feeling light-headed, dizziness, fainting;
- skin rash and tingling, swelling of the mouth or throat, difficulties breathing, wheezing;
- abnormal heart rate, chest pain, blueness of the lips or tips of the fingers and toes;
- blurred vision.

The 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 symptoms during the infusion, tell your doctor or nurse immediately. They 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 appropriate speed. Your doctor or nurse will advise you regarding the appropriate infusion speed if 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 received the last **HyQvia** infusion.
  In such cases, you will be closely monitored during your first infusion and for the first hour after your infusion has been completed.

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

Home treatments
Before you start home treatment, you should assign one person as a guardian. You and your guardian will be trained to detect early signs of side effects, especially allergic reactions. The guardian should help you pay attention to potential side effects. During the infusion, you must pay attention to the first signs of side effects (for further details see section 4 "**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** directly into or around infected, red or swollen areas on the skin, because this may cause the infection to spread.

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

Effects on blood tests

HyQvia contains many different antibodies, some of which may affect blood tests (serological tests). Tell your doctor about your treatment with **HyQvia** before performing 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 produced from human blood plasma (the liquid component of blood). When medicines are produced from human blood or plasma, certain measures are taken to prevent transmission of infections to patients. These measures include:

- careful selection of blood and plasma donors to ensure exclusion of donors who are at risk of carrying infectious diseases;
- testing of each blood donation and pools of plasma donations for signs of viruses/infections.

Manufacturers of these blood products also perform actions intended to remove or inactivate viruses while processing the blood or plasma. Despite all these measures, when medicines prepared from human blood or plasma are used, the possibility of transmitting an infection cannot be totally excluded. This also applies to any unknown or newly 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 found to be associated with hepatitis A or parvovirus B19 infections, possibly because the antibodies against these infections, which are contained in **HyQvia**, are protective against these diseases.

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;
- the injected volume, flow rate, the number and location of infusion sites.

Children and adolescents

The same indications, doses and frequency of infusion applicable for adults also apply for children and adolescents (aged 0-18 years).

Drug interactions:

If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.

Vaccines

HyQvia may reduce the effect of some vaccines against viruses 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 a measles vaccine.
Please tell your vaccinating doctor or nurse about your treatment with **HyQvia**.

Pregnancy, breastfeeding and fertility

The data on the effects of long-term use of recombinant human hyaluronidase on pregnancy, breastfeeding and fertility are limited. **HyQvia** should only be used by pregnant and breastfeeding women after consultation with a doctor.

Driving and using machines

Patients may experience side effects (such as dizziness or nausea) during treatment with **HyQvia**, that might affect the ability to drive or operate machines. If this happens, you should wait until the reactions resolve.

Important information about some of this medicine's ingredients

HyQvia contains 5.0-60.5 mg sodium (main component of cooking/table salt) in each recombinant human hyaluronidase vial. This quantity is equivalent to 0.25-3% of the maximal daily dietary intake of sodium recommended for an adult by the World Health Organization (WHO). The **HyQvia** vial of 10% human normal immunoglobulin is considered to be essentially sodium-free.

3. How to use HyQvia?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
Only your doctor will determine your dose and how you should take this medicine.

HyQvia is administered by subcutaneous (SC) infusion.

Treatment with **HyQvia** will be started by your doctor or nurse, but you may be allowed to use this 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 together if you can use **HyQvia** at home. Do not begin treatment with **HyQvia** at home until you have received all the instructions.

Dosing
Your doctor will calculate the correct dose for you based on your body weight, any previous treatment you may have already 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 dosage at 1-week intervals. This dosage will be gradually increased to larger doses at 3 to 4-week intervals between infusions. Sometimes your doctor may recommend that larger doses are split and given at two sites simultaneously. Your doctor may also adjust your dosage 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 supervised carefully throughout the infusion and for at least 1 hour after stopping the infusion to check your tolerance to the medicine. In the beginning, your doctor or nurse will use a slow infusion rate and gradually increase it during the first infusion and in the following infusions. Once the doctor or nurse has found the right dose and infusion rate for you, you may be allowed to perform the treatments by yourself at home.

Home treatments
You will receive training including:
- Germ-free (aseptic) infusion techniques;
- Use of an infusion pump or syringe driver (if needed);
- Keeping a treatment diary;
- Measures to be taken in case of severe side effects.

You must carefully follow your doctor’s instructions regarding the dosage, infusion rate and schedule for infusing **HyQvia**, so that your treatment is efficient for you.

	Patients weighing less than 40 kg		**Patients weighing 40 kg or more**	
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 2-3 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

In case of leakage at the infusion site
Ask your doctor, pharmacist or nurse if another needle size would be more appropriate for you. Any change of needle size should be supervised by the attending doctor.

If you have accidentally taken HyQvia at a dosage higher than you should
If you think that you used more **HyQvia** than you should, talk to your doctor as soon as possible.

If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately go to a hospital emergency room and bring the medicine package with you**.**

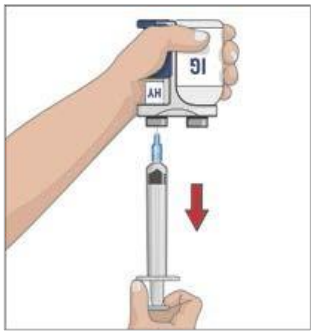
If you forget to use HyQvia
Do not infuse a double dose of **HyQvia** to compensate for a missed dose. If you think that you have missed a dose of **HyQvia**, talk to your doctor as soon as possible.

Do not exceed the recommended dose.
Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop treatment with this medicine without consulting your doctor.
Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

Detailed Instructions for Use are provided in the section below:

	1. Take HyQvia out of the box:
	• Allow the vials to reach room temperature. This may take up to 60 minutes. Do not use heating devices, including microwave.
	• **Do not heat or shake HyQvia.**
	• *Check each vial of **HyQvia** before use*:
	  • **Expiration date**: Do not use after the expiration date.
	  • **Color**:
	  ○ Recombinant human hyaluronidase should be clear and colourless.
	  ○ Human normal immunoglobulin 10% should be clear to opaque, colourless to pale yellow.
	  ○ If either liquid is cloudy or contains particles, do not use the medicine.
	  • **Cap:** Purple protective cap is on the dual vial unit. Do not use the product if it does not have the cap.

	**2. Collect all supplies:** Collect all the items required for infusion. Items include: dual vial unit(s) of **HyQvia**, infusion set components (subcutaneous needle set, solution container (bag or syringe), sterile clear bandage and tape, pump tubing, transfer devices, syringes, gauze and tape), sharps container, pump, treatment diary and other items as needed.
	3. Prepare a clean work area.
	**4. Wash your hands:** Wash your hands thoroughly. Place all the collected supplies and open them as instructed by the doctor/nurse.
	**5. Open the dual vial unit(s):** • Remove the purple protective cap and make sure the blue vial caps have been also 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 as instructed, and allow the stoppers to air dry (for at least 30 seconds).

<table>
<tr>
<td>  </td>
<td>6. Prepare the recombinant human hyaluronidase vial (HY):
• Remove the smaller sterile syringe from the package and attach it to a needle or a non-vented spike (device).
• Pull the plunger, fill the smaller syringe with air at a volume equal to the volume of recombinant human hyaluronidase in the HY vial(s).
• Remove the cap of the needle/non-vented transfer device.
• Insert the tip of the needle/non-vented transfer device into the center of the vial stopper and push straight downwards. 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 is pointing upwards.
• 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 the dose prescribed for you.
• If possible, combine the entire amount of recombinant human hyaluronidase needed for the full dose of IgG into the same syringe.
• Point the syringe tip upwards and remove any air bubbles by gently tapping the syringe with your finger. Slowly and carefully push the plunger to remove any remaining air.</td>
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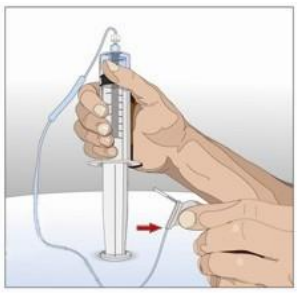
<tr>
<td>  </td>
<td>7. Prepare the needle set with the recombinant human hyaluronidase (HY):
• Attach the syringe filled with recombinant human hyaluronidase to the needle set.
• Push the plunger of the smaller syringe to remove the air and fill the needle set up to the needle wings with the recombinant human hyaluronidase.
• Note: Your doctor or nurse may recommend using a “Y” connector (for more than one site) or another needle set configuration.</td>
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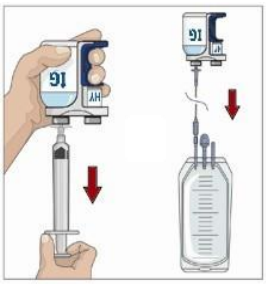
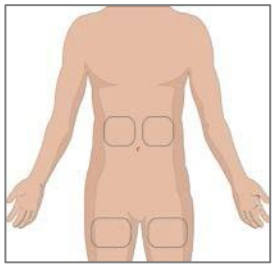
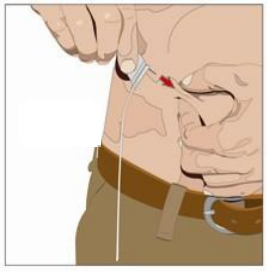
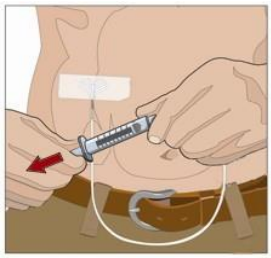
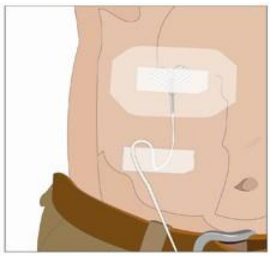
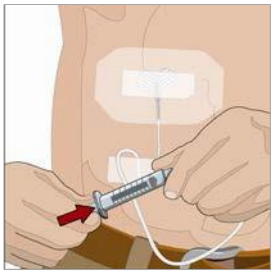
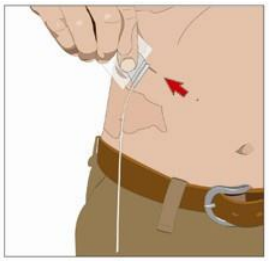
(**a**) (**b**) 	**8. Prepare the human normal immunoglobulin 10% vial:** • Prepare to transfer the immunoglobulin 10% component of **HyQvia** by wiping each vial stopper with an alcohol swab as instructed and allow the stoppers to air dry (for at least 30 seconds). • The human normal immunoglobulin 10% of **HyQvia** may be infused in two manners: ○ by drawing from the vials either into a large syringe **(a)** or an infusion bag **(b)** as instructed by the doctor or nurse, depending on the pump to be used; or ○ directly from the human normal immunoglobulin 10% vial. Insert the spike of the vented pump tubing or the spike and venting needle into human normal immunoglobulin 10% vial(s). Fill the infusion pump tubing and set aside until administration of the recombinant human hyaluronidase infusion has been completed. • If more than one vial is required for a full dose, spike the additional vials only after infusion of the entire content of the first vial has been completed.
	9. Prepare the pump: Follow the manufacturer's instructions for preparing the pump.
 	**10. Prepare the infusion site:** • Choose an infusion site(s) in either the middle to upper 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 exceeding 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 for the next infusion. • If instructed by the doctor or nurse, clean the infusion site(s) with an alcohol swab. Allow to air dry (for at least 30 seconds).
90-degree angle to skin 	**11. Insert the needle:** • Remove the needle cover. Grasp and hold a skin fold of at least 2 to 2.5 cm between two fingers. • Insert the needle completely to the wings of the needle with a rapid motion straight into the skin at a 90-degree angle. The wings of the needle should lay flat on the skin. • Secure the needle in place with a sterile tape. • Repeat this step if you have a second infusion site.

	**12. Check for proper needle placement before starting the infusion, as instructed by your healthcare professional.**
	**13. Secure the needle to the skin:** • Secure the needle(s) in place by placing a sterile bandage over the needle. • Check the infusion site(s) occasionally to ensure that there is no leakage or needle dislodgement.
	**14. Administer the recombinant human hyaluronidase first:** • Slowly push the plunger of the smaller syringe with the recombinant human hyaluronidase at an initial infusion rate per infusion site of approximately 1 to 2 ml per minute and increase the rate 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 the rate as tolerated.
	15. Administer the human normal immunoglobulin 10%: After infusing the entire content of the small syringe (recombinant human hyaluronidase), remove the syringe from the hub of the needle set. Attach the pump tubing or the large 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 doctor and start the infusion.
	16. Flush the pump tubing after completing the infusion as instructed by the doctor or nurse: • If instructed by the doctor or nurse, attach a saline bag to the pump tubing/needle set to push the residual human normal immunoglobulin 10% up to the needle wings.

	**17. Remove the needle set:** • Remove the needle set by loosening the bandage at 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. o Dispose of the sharps container according to the instructions provided with the container, or contact the doctor or nurse for instructions.
	18. Record the infusion: • Remove the label from **HyQvia** vial, which indicates the product batch number and expiration date, and place the label in your treatment record diary. • Write the date, time, dose, site(s) of infusion (to assist in changing the site for the next infusion) and any reaction that occurred after each infusion. • Throw away any unused product remaining in the vial and the disposable supplies as recommended by the doctor or nurse. • Continue follow up with your doctor as instructed by him.

4. Side effects

Like with all medicines, using **HyQvia** may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.
Certain side effects, such as headache, chills, or aches at various body areas, may be reduced by slowing the infusion rate.

Serious side effects
Infusions of medicines like **HyQvia** can occasionally cause serious, but rare, allergic reactions. You may experience a sudden drop in blood pressure and, in isolated cases, an anaphylactic shock as well. 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, dizziness or fainting, skin rash and tingling, swelling of the mouth or throat, difficulties 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 administering **HyQvia** at home, you must perform the infusion in the presence of a person assigned as a guardian, who will help you identify allergic reactions, stop the infusion, and call for help if necessary.
- Please also see section 2 in this leaflet regarding the risk of allergic reactions and home treatments with **HyQvia**.

Very common side effects (may occur in more than 1 in 10 infusions):
Infusion site pain, including mild to moderate discomfort and tenderness. These effects usually resolve within a few days.

Common side effects (may occur in up to 1 in 10 infusions):
Infusion site reactions: These include redness, swelling, itching, hardening, and rash at the infusion site. These effects usually resolve within a few days. Headache, tiredness, nausea, vomiting, diarrhoea, abdominal pain, joint or muscle pain, chest pain, fever, feeling weak or unwell.

Uncommon side effects (may occur in up to 1 in 100 infusions):
Chills, migraine, increased blood pressure, dizziness, abdominal bloating, skin rash/allergic rash/redness, tingling, pain in the 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.

Side effects of unknown frequency (the frequency of these effects has not been established yet):
Hypersensitivity, influenza-like illness, infusion site leakage and inflammation of the brain meninges (aseptic meningitis).

Side effects observed with similar medicines
The following side effects have been observed with infusion of medicines like human normal immunoglobulin 10% administered subcutaneously. Although these side effects have not yet been observed with **HyQvia**, they may also occur in people treated with **HyQvia**:
Trembling, oral tingling, fast heart rate, allergic reactions, flushing or pallor, cold hands or feet, shortness of breath, swelling of face, excessive sweating, muscle stiffness, changes in liver function blood tests (increase in alanine aminotransferase).

The following rare side effects have been observed in patients using medicines like human normal immunoglobulin 10% administered intravenously. These reactions have not been observed with **HyQvia**, but there is a low probability that they may occur in people treated with **HyQvia**:
Blood clots in blood vessels (thromboembolic reactions) leading to heart attack, stroke, deep vein thrombosis, or thrombosis in blood vessels supplying blood to the lungs (pulmonary embolism), kidney diseases or renal failure, destruction of red blood cells (hemolysis).

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions:
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 contain particles or deposits. After opening, dispose of any unused solutions remaining 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. Additional information

In addition to the active ingredient, this medicine also contains:
- In a vial of human normal immunoglobulin 10%: glycine, water for injection
- In a vial of recombinant human hyaluronidase:
  recombinant human hyaluronidase (rHuPH20), sodium phosphate dibasic dihydrate, sodium hydroxide, human serum albumin 25%, calcium chloride dihydrate, sodium chloride, edetate disodium dihydrate, 25% hydrochloric acid, water for injection

What the medicine looks like and contents of the pack:
The product unit is a dual vial:
- a solution of recombinant human hyaluronidase (Step 1 of **HyQvia** / Infused first)
  Recombinant human hyaluronidase is a clear colourless solution with no particles.
- a solution of human normal immunoglobulin 10% (Step 2 of **HyQvia** / Infused second).
  1 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 ingredient of **HyQvia** is human normal immunoglobulin. This medicine also contains trace amounts of immunoglobulin A (IgA) (no more than 140 micrograms/ml, 37 micrograms on the average).

Human normal immunoglobulin 10% is a clear to slightly opaque, colourless to pale yellow solution.

The following pack sizes are available:

Recombinant human hyaluronidase	**Human normal immunoglobulin 10%**

Volume (ml)	Protein (gram)	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.

Registration holder's name and address: Takeda Israel Ltd., 25 Efal St., Petach Tikva 4951125

Manufacturer's name and address:
Baxalta Belgium Manufacturing SA, Lessines, Belgium

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 160-21-35267-00

This leaflet was revised in August 2022 according to the Ministry of Health guidelines.