Patient leaflet in accordance with Pharmacist's Regulations (Preparations) 1986

The medicine is marketed according to doctor's prescription only.

Hizentra, 200 mg/ml solution for subcutaneous infusion in vial
Hizentra, 200 mg/ml solution for subcutaneous infusion in pre-filled syringe

Human normal immunoglobulin (SCIg = Subcutaneous Immunoglobulin)

Composition

The **active substance** is human normal immunoglobulin. One ml contains 200 mg of human normal immunoglobulin, of which at least 98% is immunoglobulin type G (IgG).

The approximate percentage of IgG subclasses is as follows:
IgG1 69 %
IgG2 26 %
IgG3 3 %
IgG4 2 %

This medicine contains trace amounts of IgA (not more than 50 micrograms /ml).
Hizentra is essentially sodium free.

Other ingredients (excipients)

See section 6.

- **Read the leaflet carefully until the end before using the medicine.**
This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or the pharmacist.
- This medicine was prescribed for you. Do not pass it on to others. It may harm them even if their medical condition seems similar to yours.

1. **What Hizentra is used for?**

Hizentra is used in the treatment of adults and children:

1. Who are born with a reduced ability or inability to produce immunoglobulins (primary immunodeficiencies). This includes conditions such as:
   - low immunoglobulin levels (hypogammaglobulinaemia) or absence of immunoglobulins (agammaglobulinaemia) in the blood
   - combination of low immunoglobulin levels, frequent infections and inability to produce adequate amounts of antibodies after vaccination (common variable immunodeficiency)
   - combination of low level or absence of immunoglobulins and absence or non-functional immune cells (severe combined immunodeficiency and Wiskott- Aldrich syndrome)
   - lack of certain immunoglobulin G subclasses causing recurrent infections.

2. Treatment of low immunoglobulin levels (Hypogammaglobulinaemia) and recurrent infections in patients with chronic lymphocytic leukaemia (CLL), a certain kind of blood cancer.

3. Treatment of low immunoglobulin levels (Hypogammaglobulinaemia) and recurrent infections in patients with myeloma, another kind of blood cancer.

What Hizentra is
Hizentra belongs to the class of medicines called human normal immunoglobulins. Immunoglobulins are also known as antibodies and are blood proteins that help your body to fight infections.

How Hizentra works
Hizentra contains immunoglobulins that have been prepared from the blood of healthy people. Immunoglobulins are produced by human body's immune system. They help your body to fight infections caused by bacteria and viruses or maintain the balance in your immune system (referred to as immunomodulation). The medicine works in exactly the same way as the immunoglobulins naturally present in your blood.

Therapeutic group: human normal immunoglobulins

2. Before using the medicine

Do **NOT** use Hizentra:
- if you are allergic to human immunoglobulins, polysorbate 80 or L-proline. Tell your doctor or healthcare professional prior to treatment if you have experienced an intolerance against one of these components earlier.
- if you suffer from hyperprolinaemia type I or II (a genetic disorder causing high levels of the amino acid proline in the blood).
- Do not inject into a blood vessel.

Special warnings regarding the use of the medicine

Talk to your doctor or healthcare professional before starting using Hizentra.

Administer Hizentra via the subcutaneous route only (under the skin). If Hizentra is accidentally administered into a blood vessel, you could develop severe allergic reaction (anaphylactic shock).

You may be allergic (hypersensitive) to immunoglobulins without knowing it. However, true allergic reactions are rare. They may occur even if you received human immunoglobulins previously and tolerated them well. It may happen particularly if you do not have enough of the immunoglobulin type A (IgA) in your blood (IgA deficiency).

- Tell your doctor or healthcare professional prior to treatment if you have an immunoglobulin type A (IgA) deficiency. Hizentra contains residual amounts of IgA which might cause an allergic reaction.
In these rare cases allergic reactions, such as a sudden fall in blood pressure or shock may occur (see also section 4 "Side effects").

- If you notice such signs during the infusion of Hizentra, stop the infusion and contact your doctor or go to the nearest hospital immediately.

- Tell your doctor if you have a history of heart or blood vessel disease or blood clots, have thick blood, or have been immobile for some time. These things may increase your risk of having a blood clot after using Hizentra. Also tell your doctor what drugs you are using, as some drugs, such as those that contain the hormone estrogen (for example, birth control pills), may increase your risk of developing a blood clot. Contact your doctor immediately if you experience signs and symptoms such as shortness of breath, chest pain, pain and swelling of a limb, weakness or numbness on one side of the body after receiving Hizentra.

- Contact your doctor if you experience the following signs and symptoms: severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting after receiving Hizentra. These symptoms might indicate aseptic meningitis (a temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord). Your doctor will decide if further tests are necessary and whether Hizentra should be continued.

Your healthcare professional will avoid potential complications by ensuring:

- that you are not sensitive to human normal immunoglobulin.
The medicine must be infused slowly at first. The recommended infusion rate given under section 3 “How should you use the medicine” must be closely followed.

- that you are carefully monitored for any symptoms throughout the infusion period, especially if:
-you receive human normal immunoglobulin for the first time
-you have switched from a different medicine to Hizentra
-there has been a long interval (more than eight weeks) since the previous infusion.

  In these cases, it is recommended that you are monitored during the first infusion and for an hour afterwards. If the points above do not apply for you it is recommended that you are observed for at least 20 minutes after administration.

Interactions with other drugs:

If you are taking, have recently taken, or might use other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

- You must not mix other medicines with Hizentra.

- Tell your vaccinating doctor prior to a vaccination about your treatment with Hizentra.
  Hizentra may impair the effect of some live virus vaccines such as measles, rubella, mumps and chicken pox. Therefore, after receiving this medicine you may have to wait up to 3 months before receiving your live-attenuated vaccine. In the case of measles vaccinations the impairment may persist for up to 1 year.

Pregnancy , breast-feeding and fertility:

- Tell your doctor or healthcare professional if you are pregnant, plan to become pregnant or are breast-feeding. Your doctor will decide whether you can receive Hizentra during your pregnancy or while you are breast-feeding.

No clinical studies have been performed with Hizentra in pregnant women. However, medicines that contain immunoglobulins have been used in pregnant or breast-feeding women for years, and no harmful effects on the course of pregnancy or on the baby have been observed.

If you are breast-feeding and receive Hizentra, the immunoglobulins of the medicine can also be found in the breast milk. Therefore, your baby may be protected from certain infections.

Driving and using machines:

Patients may experience effects, such as dizziness or nausea, during treatment with Hizentra that might affect the ability to drive and use machines. If this happens, you should not drive or use machines until these effects have disappeared.

Important information on some of the ingredients of the medicine:

Hizentra contains proline.
You must not take it if you suffer from hyperprolinaemia type I or II (see also section 2 “Before using the medicine”). Please tell your doctor prior to treatment.

<u>Other important information about Hizentra</u>

<u>Blood tests</u>
After receiving Hizentra, the results of certain blood tests (serological tests) may be impaired for a certain time.
- Tell your doctor about your treatment with Hizentra prior to any blood test.

<u>Information on what Hizentra is made of</u>
Hizentra is made from human blood plasma (this is the liquid part of the 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 virus/ infections.

Manufacturers of these medicines 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 administered, 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 are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus and hepatitis C virus (liver inflammation), and for the non-enveloped hepatitis A virus and parvovirus B19.

- It is strongly recommended that every time you receive a dose of Hizentra the name and batch number of the product are recorded in order to maintain a record of the batches used (see section 3 “How should you use the medicine”).

3. How should you use the medicine?

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The dosage and treatment regimen will be determined by the doctor only.

Dosage
Your doctor will calculate the correct dose for you taking into account your weight and response to treatment.

Your doctor may adjust the dose based on your response to the treatment.
Your doctor will determine whether you need a loading dose (for adults and children) of at least 1 to 2.5 ml/kg of body weight divided over several days. Following this, maintenance doses may be given at repeated intervals, from daily to once every two weeks, to reach a cumulative monthly dose of about 2 to 4 ml/kg of body weight.

Do not change the dose or dosing interval without consulting with your doctor. If you think you should receive Hizentra more or less frequently, please speak to your doctor.
If you think you have missed a dose, speak to your doctor as soon as possible.

Do not exceed the recommended dosage.

Method and route of administration
In case of home treatment, this will be initiated by a healthcare professional experienced in the treatment of immunodeficiency and in the guidance of patients for home treatment.

You will be instructed in:
- aseptic infusion techniques
- the keeping of a treatment diary, and
- measures to be taken in case of severe side effects.

Only after such guidance should you follow the instructions below.

Infusion site(s)

- Administer Hizentra under the skin only.
- You may inject Hizentra into sites such as abdomen, thigh, upper arm, and lateral hip. If large doses are given (>25 ml), try to administer them at multiple sites.
- You may use up to 4 injection sites simultaneously. Injection sites should be at least 5 cm apart.
- In the case, you will use a device-assisted infusion technique (e.g. pump-assisted infusion), more than one infusion device can be used simultaneously.
- In the case, you will use the manual push infusion technique with a syringe, you may use only one infusion site per syringe. If you need to administer an additional Hizentra syringe, you must use a new sterile injection needle and change the infusion site.

- The volume of product infused into a particular site may vary.

Infusion rate (s)

Your doctor will determine the appropriate infusion technique and the infusion rate for you taking into account your individual dose, dosing frequency and product tolerability.

The recommended initial infusion rate is up to 15 ml/hour/site. If well-tolerated, you may gradually increase the infusion rate to 25 ml/hour/site.

Instructions for use

- If you use Hizentra vials - please see "instructions for vial users" at the end of this leaflet.
- If you use Hizentra pre-filled syringes - please see "instructions for pre-filled syringes users" at the end of this leaflet.

If you have accidentally taken a higher dosage

If you think you have had too much Hizentra, speak to your doctor as soon as possible.

If you have forgotten to take the medicine

If you think you have missed a dose, speak to your doctor as soon as possible.

You should complete the treatment recommended by the doctor. Even if an improvement in your state of health has begun, do not stop treatment with the medicine without consulting with a doctor.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.

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

4. Side effects

As with all medicines, the use of Hizentra may cause side effects in some users. Do not be alarmed at reading the list of side effects. You may not suffer from any of them.

- ► In isolated cases, you may be allergic (hypersensitive) to immunoglobulins and allergic reactions such as a sudden fall in blood pressure or shock may occur (e.g. you may feel light- headed, dizzy, faint on standing, cold in the hands and feet, sense an abnormal heart beat or chest pain, or have blurred vision).

- ► In isolated cases, you may experience pain and/ or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body, sudden confusion, or trouble speaking or understanding could be signs of a blood clot.

- ► In isolated cases, you may get a bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light, which could be signs of AMS (aseptic meningitis syndrome), which is a temporary reversible non-infectious inflammation of the membranes surrounding the brain and the spinal cord.

  → If you notice such signs during the infusion of Hizentra, stop the infusion and go to the nearest hospital immediately.

Please see also section 2 of this leaflet about the risk of allergic reactions, blood clots and AMS.

The following side effects observed in controlled clinical studies are presented in order of decreasing frequency. Side effects observed in post-marketing are of unknown frequency:

The following side effects are **very common** (affects more than 1 patient in 10):
- Headache
- Rash
- Reactions at the infusion site

The following side effects are **common** (affects 1 to 10 patients in 100):
- Dizziness
- Migraine
- Increased blood pressure (hypertension)
- Diarrhoea
- Abdominal pain
- Feeling sick (nausea)
- Vomiting
- Itching (pruritus)
- Hives (urticaria)

- Pain related to the musculature and bones (musculoskeletal pain)
- Joint pain (arthralgia)
- Fever
- Tiredness (fatigue), including generally feeling unwell (malaise)
- Chest pain
- Flu-like symptoms
- Pain

The following side effects are **uncommon** (affects 1 to 10 patients in 1,000):
- Hypersensitivity
- Involuntary shaking movements in one or more parts of the body (tremor, including psychomotor hyperactivity)
- Fast heartbeat (tachycardia)
- Flushing
- Muscle spasm
- Muscular weakness
- Chills, including low body temperature
- Abnormal result of blood tests that may indicate impaired liver and kidney functions

In isolated cases, infusion site ulcer or burning sensation may

occur.

→You may reduce possible side effects if you infuse Hizentra slowly.

Side effects such as these may occur even when you have previously received human immunoglobulins and tolerated them well.

Please also refer to section 2 “Before using the medicine” for additional details on circumstances which increase the risk of side effect.

If you get a side effect, if one of the side effects worsen, or when you suffer from a side effect that is not mentioned in this leaflet, consult with the doctor.

Reporting of side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Reporting Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il)
, which links to an online form for reporting side effects, or by the following link:

https://sideeffects.health.gov.il/

In addition, you can report by emailing the Registration Holder's Patient Safey Unit at:
PV-IL@cslbehring.com

5. How should the medicine be stored?

- Avoid poisoning!

This medicine and all other medicines should be stored in a closed place out of the reach and sight of children and/ or infants in order to avoid poisoning.
Do not induce vomiting unless explicitly instructed by a doctor to do so.

- Do not use this medicine after the expiry date which is stated on the outer carton and the vial or the pre-filled syringe label after EXP.

The expiry date refers to the last day of that month.

Storage conditions:

- Because the solution contains no preservative, you must use/ infuse it as soon as possible after opening the vial or the blistered pre-filled syringe.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial or the blistered pre-filled syringe in the outer carton in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active substance, the medicine also contains:
The other ingredients (excipients) are: L-proline, polysorbate 80 and water for injections.

- What does the medicine look like and contents of the pack:
Hizentra is a clear solution for subcutaneous injection (200 mg/ml). The colour can vary from pale-yellow to light-brown.

Hizentra is available in vials of 5, 10, 20 or 50 ml.
Hizentra is also available in pre-filled syringes of 5 and 10 ml

Pack sizes
Packs of 1 vial or pre-filled syringe.

Please note that alcohol swabs, needles and other supplies or equipment are not contained in the pack.

Not all pack sizes may be marketed.

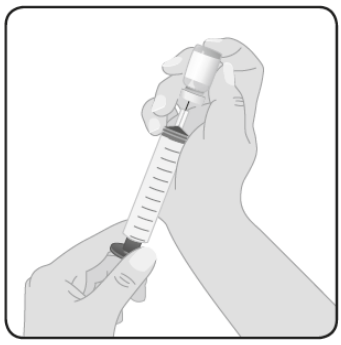
Registration holder:
CSL BEHRING LTD.,
4 Dolev st., Ra'anana 4366204

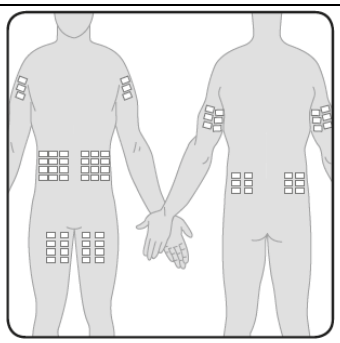
Manufacturer:
CSL Behring AG

Wankdorfstrasse 10
CH-3014 Bern, Switzerland

Registration number of the medicine in the National Drug Register in the Ministry of Health: 164-52-35308-00

Instructions for Vial users

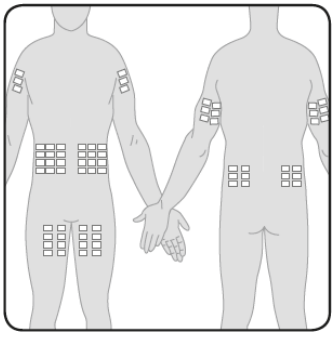
Follow the steps below and use aseptic technique to administer Hizentra.	
1	**Clean surface** Thoroughly clean a table or other flat surface using an antiseptic wipe.
2	**Assemble supplies** Place Hizentra and other supplies and equipment needed for the infusion on a clean, flat surface.
3	**Thoroughly wash and dry hands**
4	**Check Vials** Visually inspect Hizentra for particles in the solution or discoloration as well as expiry date before administering Hizentra**.** Do not use solutions that are cloudy or contain particles. Do not use solutions that have been frozen. Administer solution which is at room or body temperature. Once a vial has been opened, use the solution immediately.
5	**Preparation of Hizentra for infusion** ***Clean the vial stopper*** – Remove the protective cap from the vial to expose the central portion of the rubber stopper. Clean the stopper with an alcohol wipe or antiseptic preparation and allow it to dry. ***Transfer Hizentra to syringe for infusion*** – Attach a transfer device or needle to a sterile syringe, using aseptic technique. If using a transfer device (spike), follow the instructions provided by the device manufacturer. If using a needle, pull back on the plunger to draw air into the syringe that is comparable to the amount of Hizentra to be withdrawn. Then, insert the needle into the center of the vial stopper and, to avoid foaming, inject air into headspace of the vial (not into the liquid). Finally, withdraw the desired volume of Hizentra. When using multiple vials to achieve the desired dose, repeat this step. 
6	**Prepare the tubing** Attach the administration tubing or needle set to the syringe. Push the syringe plunger to eliminate all the tubing remaining air.

7	**Prepare infusion site(s)** **Select the infusion site(s) –** The number and location of infusion sites depends on the volume of the total dose. Each infusion site should be at least 5 cm apart. You may use up to 4 infusion sites simultaneously.  **Clean the infusion site(s)** using an antiseptic skin preparation, Allow each site to dry before proceeding.
8	**Insert the needle** Grasp the skin between 2 fingers and insert the needle into the subcutaneous tissue.  **Secure the needle to the skin** – If necessary, use gauze and tape or transparent dressing to hold the needle in place.
9	**Infuse Hizentra** Start infusion. If using an infusion pump, follow the manufacturer's instructions.
10	**Record the infusion** Record the following data in your treatment diary: • the date of administration, • the batch number of the medicine, and • the infused volume, flow rate, the number and location of infusion sites.
11	**Clean up** Discard any unused product and all used administration supplies after administration in accordance with the instructions you received.

If you have any further questions on the use of this medicine, please ask your doctor or healthcare professional.

<u>Instructions for pre-filled syringes users</u>

Follow the steps below and use aseptic technique to administer Hizentra.	
1	**Clean surface** Thoroughly clean a table or other flat surface using an antiseptic wipe.
2	**Assemble supplies** Place Hizentra and other supplies and equipment needed for the infusion on a clean, flat surface.

3	**Thoroughly wash and dry hands**
4	**Check blistered pre-filled syringes** Visually inspect Hizentra for particles in the solution or discoloration as well as expiry date before administering Hizentra**.** Do not use solutions that are cloudy or contain particles. Do not use solutions that have been frozen. Administer solution which is at room or body temperature. Once a blistered pre-filled syringe has been opened, use the solution immediately.
5	**Preparation of Hizentra for infusion** The 5 ml and 10 ml pre-filled syringes are supplied fully assembled and ready to use.  All pre-filled syringes have a standard luer lock, which is a screw connection at the syringe tip that creates a leak-free seal. If you are using a syringe pump, Hizentra pre-filled syringes can be placed directly in the syringe pump if the syringe size matches the pump requirements. If the pre-filled syringe can be placed directly on the pump, then go to Step 6. If the Hizentra pre-filled syringe size does not match the pump requirements, then the contents of the pre-filled syringe can be transferred to another syringe of a size specific for the pump.
6	**Prepare the tubing** Attach the administration tubing or needle set to the syringe. Prime the tubing to eliminate all remaining air.
7	**Prepare infusion site(s)** **Select the infusion site(s) –** The number and location of infusion sites depends on the volume of the total dose. Each infusion site should be at least 5 cm apart. You may use up to 4 infusion sites simultaneously.  **Clean the infusion site(s)** using an antiseptic skin preparation, Allow each site to dry before proceeding.
8	**Insert the needle** Grasp the skin between 2 fingers and insert the needle into the subcutaneous tissue.

	Secure the needle to the skin – If necessary, use gauze and tape or transparent dressing to hold the needle in place. 
9	**Infuse Hizentra** Start infusion. If using an infusion pump, follow the manufacturer's instructions.
10	**Record the infusion** Record the following data in your treatment diary: • the date of administration, • the batch number of the medicine, and • the infused volume, flow rate, the number and location of infusion sites.
11	**Clean up** Discard any unused product and all used administration supplies after administration in accordance with local requirements.

If you have any further questions on the use of this medicine, please ask your doctor or healthcare professional.

Revised in December 2023 according to MoH guidelines.

CSL Behring