

HIZENTRA[®] Solution for Subcutaneous Injection

Human Normal Immunoglobulin 200 mg/ml

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What Hizentra is used for

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.

Replacement Therapy

Hizentra is used to raise abnormally low immunoglobulin levels in your blood to normal levels (replacement therapy). The medicine is used in the following situations:

- Treatment of adults, and children and adolescents (0-18 years) who are born with a reduced ability or inability to produce immunoglobulins (primary immunodeficiency syndromes). 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)
- Treatment of adults and children

with certain kinds of blood cancer (such as multiple myeloma (MM) or chronic lymphocytic leukaemia (CLL)) which lead to severely low immunoglobulin levels in the blood and cause recurrent infections.

Immunomodulatory therapy in CIDP patients

Hizentra is also used in patient (adult and children and adolescents (0-18 years) with chronic inflammatory demyelinating polyneuropathy (CIDP), a form of autoimmune disease. CIDP is characterized by chronic inflammation of the peripheral nerves that causes muscle weakness and/or numbness mainly in the legs and arms. It is believed that the body's defenses attack underlines such inflammation, and immunoglobulins present in Hizentra help to protect the nerve from being attacked (immunomodulatory therapy).

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 to fight infections caused by eg: 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.

Before you use Hizentra

- When you must not use it:
 - Do not infuse Hizentra if you were allergic to human immunoglobulins, polysorbate 80 or L-proline in the past. Tell your doctor or healthcare professional prior to treatment if you have experienced intolerance against one of these components earlier
 - Do not infuse Hizentra if you

suffer from hyperprolinaemia (a genetic disorder causing high levels of the amino acid proline in the blood).

- Before you start to use it

Talk to your doctor or healthcare professional before using Hizentra.

Route of administration

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).

The infusion rate recommended by your doctor should be adhered to. Closely monitor and carefully observe for any adverse events throughout the infusion period.

Hypersensitivity / Anaphylaxis

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

Your doctor will avoid potential complications by ensuring:

- that you are not sensitive to human normal immunoglobulin.
- the medicine must be infused slowly

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at first.

- 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
 - 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.

Blood clots

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.

Aseptic Meningitis Syndrome (AMS)

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.

Pathogen safety

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 additional 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. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with Hizentra and it is also assumed that the antibody content makes an important contribution to the viral safety.

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.

Taking other medicines

Tell your doctor if you are using, have recently used or might use any other medicines. You must not mix other medicines with Hizentra.

- Live attenuated virus vaccines

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.

Blood Test

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.

Pregnancy, breastfeeding and fertility

Tell your doctor if you are pregnant, plan to become pregnant or are breastfeeding. Your doctor will decide whether you can receive Hizentra during your pregnancy or while you are breastfeeding. No clinical studies have been performed with Hizentra in pregnant women. However, medicines that contain immunoglobulins have been used in pregnant or breastfeeding women for years, and no harmful effects on the course of pregnancy or on the baby have been observed. If you are breastfeeding 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

No effects of Hizentra on the ability to drive and use machines are expected.

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Hizentra contains proline

You **must not** take it if you suffer from hyperprolinaemia (see also “before you start to use it”) Please tell your doctor prior to treatment.

How to use Hizentra

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

- How much to use

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

Replacement therapy:

Your doctor will determine whether you need a loading dose (for adults, and children and adolescents) of at least 1 to 2.5 ml/kg of body weight that may be 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. Your healthcare professional may adjust the dose based on your response to the treatment.

Immunomodulatory therapy

The therapy with Hizentra is initiated 1 week after the last IVIg infusion. The recommended subcutaneous dose is 0.2 to 0.4 g/kg bw per week. The weekly dose can be divided into smaller doses and administered by desired number of times per week. For dosing every two weeks, double the weekly Hizentra dose. The dose may need to be adapted to achieve the desired clinical response. Patient's

individual clinical response should be the primary consideration in dose adjustment.

If CIDP symptoms worsen on 0.4 g/kg bw per week, re-initiating therapy with IGIV should be considered, while discontinuing HIZENTRA.

Hizentra maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Maintenance therapy beyond these periods should be individualized based upon the patient's response and need for continued therapy

- When to use it

Use as directed by your doctor.

- How long to use it

Use as directed by your doctor.

- If you forget to use it

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

- If you use too much (overdose)

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

While you are using it

- Things you must do

In case of home treatment, this will be initiated and initially monitored by a healthcare professional experienced in the treatment of immunodeficiency/ CIDP 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.

- Administer Hizentra **under the**

skin only.

- You may infuse Hizentra into sites such as abdomen, thigh, upper arm, and lateral hip (see Figure 1). If large doses are given (> 50 ml), try to administer them at multiple sites.
- There is no limit to the number of infusion sites used at the same time.
- More than one infusion device can be used simultaneously.
- The volume of product infused into a particular site may vary.
- Infusion sites should be at least 5 cm apart.



Figure 1: Possible infusion sites for Hizentra

The recommended initial infusion rate is up to 20 ml/ hour/ site. If well-tolerated, you may gradually increase the infusion rate to 35 ml/ hour/ site for the following two infusions. Thereafter, the infusion rate can be further increased as per your tolerability. If you are a patient at a risk, as described in “Before you start to use it”, administer Hizentra at the minimum dose and infusion rate practicable.

- Things you must not do

- Do not use solutions that are cloudy or contain particles.
- Do not use solutions that have been frozen

- Things to be careful of

- Hizentra is a ready-to-use solution. (see “Storage” and “Product Description”)
- Administer solution which is at room temperature (25°C)
- Once a vial/blistered pre-filled syringe has been opened, use the solution immediately.

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- Use aseptic technique when preparing and administering Hizentra
- 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.

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

Possible Side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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

Very common side effect (affects more than 1 patient in 10):

- Nasopharyngitis
- Headache, including migraine
- Rash
- Pain related to musculature and bones (musculoskeletal pain), including muscle spasm and muscular weakness
- Reactions at the injection site

Common side effects (affects 1 to 10 patients in 100):

- Dizziness
- Increase blood pressure (hypertension)
- Diarrhoea
- Abdominal pain
- Feeling sick (nausea)
- Vomiting
- Itching (pruritus)
- Skin Reaction such as blistering (urticaria)
- Joint pain (arthralgia)
- Fever
- Tiredness (fatigue), including generally feeling unwell

- (malaise)
- Chest pain
- Flu-like symptoms
- pain

Uncommon Side effects (affects 1 to 10 patients in 1,000):

- Hypersensitivity
- Aseptic meningitis syndrome (AMS, a temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord)
- Tremor, including psychomotor hyperactivity
- Fast heartbeat (tachycardia)
- Flushing
- Chills, including low body temperature
- Results of blood tests suggesting impaired liver and kidney function

SI isolated cases (post-marketing experience) hypersensitivity and anaphylactic reactions of the immune system, burning sensation, formation of blood clots which may be carried off in the blood circulation and which may result in blockage of blood vessel (embolic and thrombotic events), and infusion-site ulcer have been observed in treatment with Hizentra.

Tell your doctor immediately if you have any of the following signs or symptoms during or following an infusion of Hizentra.

- 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).

If you notice such signs during the infusion of Hizentra, tell your doctor immediately. Please see also section 2 of this leaflet about the risk of allergic reactions.

You may reduce or even avoid possible side effects if you slowly infuse Hizentra.

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.

- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light could be signs of AMS.

If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my [Consumers Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)]

Storage and Disposal of Hizentra

- Storage

- Do not use this medicine after the expiry date (EXP) which is stated on the outer carton and the vial/blistered pre-filled syringe label after EXP.
- Hizentra should be administered as soon as possible after opening the vial/blistered pre-filled syringe as the solution contains no preservative.
- Do not store above 25 °C.
- Do not freeze.

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- **Keep this medicine out of the sight and reach of children.**
- Keep the vial or the blistered pre-filled syringe in the outer carton in order to protect from light.

- Disposal

- Do not throw away any medicines via waste water or household waste.
- Ask your doctor or healthcare professional how to throw away medicines you no longer use. These measures will help protect the environment.

Product Description

- What it looks like Hizentra is provided as a ready-to-use sterile solution in single-use vials or single-use pre-filled syringes.
- 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 or pre-filled syringes of 5, 10, 20 or 50 ml.

Pack sizes

Packs of 1, 10 or 20 vials.
Packs of 1 or 10 pre-filled syringes.
Not all pack sizes may be marketed.

- Ingredients

The **active substance** is human normal immunoglobulin. One ml contains 200 mg of human plasma protein (20 % solution), 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).

The **other ingredients** (excipients) are L-proline, polysorbate 80 and

water for injections.

Hizentra is essentially sodium free.

Hizentra contains no preservatives.

- MAL number:

MAL18016154ARZ

Manufacturer

CSL Behring AG, Bern, Switzerland

Product Registration Holder

DKSH Malaysia Sdn Bhd
B-11-01, The Ascent Paradigm,
No.1, Jalan SS7/26A Kelana Jaya
47301 Petaling Jaya Selangor .

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- March 2020

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NPRA (R3/01) 06072020/0091

Instructions for use

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 (vented 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



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6. Prepare the tubing

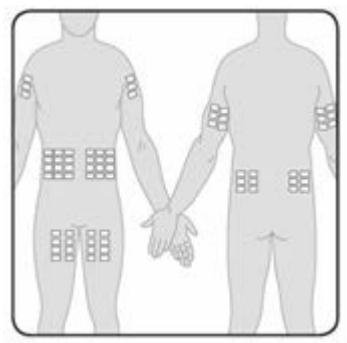
Attach the administration tubing or needle set to the syringe. Prime the tubing to eliminate all remaining air.

7. Prepare infusion site(s)

Select the infusion site(s) – The number and location of injection sites depends on the volume of the total dose. Each infusion site should be at least 5 cm apart.

You may use an unlimited number of 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.