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MEA/EN MULTI MARKET MANUSCRIPT DATA SHEET

VIAL

HIZENTRA®

Revision date: 19-Oct-2022
Reason for change: SID indication update

Supersedes previous version(s):
JAN-2021 – CCDS update V6.0
16-APR-2019-CCDS updates V4.0 and V5.0

Note:

- Headers and footers will not be printed.
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1. Name of the medicinal product

Hizentra ®

200 mg/ml solution for subcutaneous injection

2. Composition

a. Active substances

Human normal immunoglobulin for subcutaneous injection (SCIg).

Human plasma protein with a minimum content of ≥98% immunoglobulin G (IgG).

Distribution of the IgG subclasses approximately: IgG_1 69%, IgG_2 26%, IgG_3 3%, IgG_4 2%.

The maximum immunoglobulin A (IgA) content is 50 micrograms/mL.

b. Excipients

L-proline, polysorbate 80, sodium hydroxide (equivalent to sodium <10 mmol/L), hydrochloric acid, water for injections.

3. Pharmaceutical form and active substance quantity per unit

Solution for injection for subcutaneous use.

1 mL solution contains: 200 mg human plasma protein with a minimum IgG content of 98% (20% solution).

The osmolality is approximately 380 mOsmol/kg.

The solution is clear. The colour may vary from pale-yellow to lightbrown.

4. Clinical particulars

4.1 Indications / Uses

Replacement therapy in adults and children in:

- Primary immunodeficiency diseases such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia
  - common variable immunodeficiency
  - severe combined immunodeficiency and Wiskott-Aldrich syndrome
  - IgG subclass deficiencies with recurrent infections

- Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG levels < 4 g/L.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre in response to pneumococcal polysaccharide and polypeptide antigen vaccines.

Immunomodulatory therapy:

- Hizentra is indicated for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), as maintenance therapy after stabilisation with immunoglobulins for intravenous administration (IVIg).

4.2 Dosage/Administration

Usual Dosage

The dose and the dosage regimen depend on the indication.

The therapy should be initiated and monitored under the supervision of a healthcare professional experienced in the IgG treatment of immunodeficiency or CIDP.

To ensure traceability of biological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

<u>Replacement therapy in adults and children</u>

The dose may need to be adjusted individually for each patient dependent on the clinical course of the disease and serum IgG trough levels. The following dosages are given as recommendations:
The aim of replacement therapy with subcutaneous Hizentra is to obtain sustained IgG levels. The starting dose is in the range of at least 0.2 – 0.5 g/kg (1.0 – 2.5 mL/kg) body weight. This dose may need to be divided over several days. The monthly maintenance dose to sustain stable IgG levels is in the order of 0.4 – 0.8 g/kg (2.0 – 4.0 mL/kg) body weight and is given in divided doses at repeated intervals (see section “Pharmacokinetics”).

For patients who are switching from intravenous therapy to subcutaneous therapy, the previous monthly dose is divided into smaller doses and administered at repeated intervals (see section “Pharmacokinetics”).

Trough levels should be measured and assessed, taking the patient’s clinical response into account. Depending on the clinical course of the disease (e.g., infection rate), adjustment of the dose and/or the dosing interval may be considered in order to achieve higher trough levels.

<u>Immunomodulatory therapy in CIDP</u>

Treatment with Hizentra is initiated 1 week after the last IVIg infusion. The recommended subcutaneous starting dose is 0.4 g/kg body weight per week. When a patient is clinically stable, the weekly dose of Hizentra can be reduced to a minimum of 0.2 g/kg body weight per week.
If there is a relapse after the dose has been reduced to 0.2 g/kg body weight per week, the subcutaneous dose should revert to the higher dose of 0.4 g/kg body weight per week. If the patient does not respond or a relapse occurs on the higher dose, the patient must be switched to IVIg with an initial loading dose. Should rescue therapy with IVIg be necessary, a return to SCIg therapy is not recommended.

The weekly dose can be divided into smaller doses and administered at the desired frequency. For dosage regimens with treatment every two weeks, the weekly dose of Hizentra has to be doubled.

The efficacy of Hizentra compared with placebo after switching from intravenous immunoglobulins has been demonstrated in clinical trials. No direct comparative data for Hizentra versus IVIg are available.

Elderly patients

As the dose is given by body weight and adjusted to the clinical response, it is not to be expected that the dose in elderly patients will differ from that in persons 18 to 65 years of age.
Hizentra was evaluated in clinical trials in 13 patients > 65 years of age with PID. No specific dose adjustments were necessary to achieve the desired serum IgG levels.
Hizentra was evaluated in clinical trials in 61 patients aged >65 with CIDP. No specific dose adjustments were necessary to achieve the desired clinical outcome.

Children and adolescents

As with adults, the dosage is related to body weight and, for replacement therapy, it is adjusted as necessary according to the clinical course of the disease. Sixty-eight children with PID aged between 2 to 12 years and 57 adolescents with PID aged 12 to <18 were treated with Hizentra. No paediatric dose adjustments were necessary to achieve the desired serum IgG levels.
Hizentra has not been evaluated in clinical trials in paediatric patients with CIDP.

Mode of administration

Hizentra is for subcutaneous use only.

Hizentra may be infused into sites such as the abdomen, thigh, upper arm and lateral hip (see figure 1). If high doses (>50 mL) are to be given, it is advisable to use several sites. For infants and children, the infusion site should be changed every 5-15 mL. There is no limit to the number of infusion sites. Infusion sites should be at least 5 cm apart. More than one infusion device can be used at the same time. The volume of product injected into a particular site may vary.

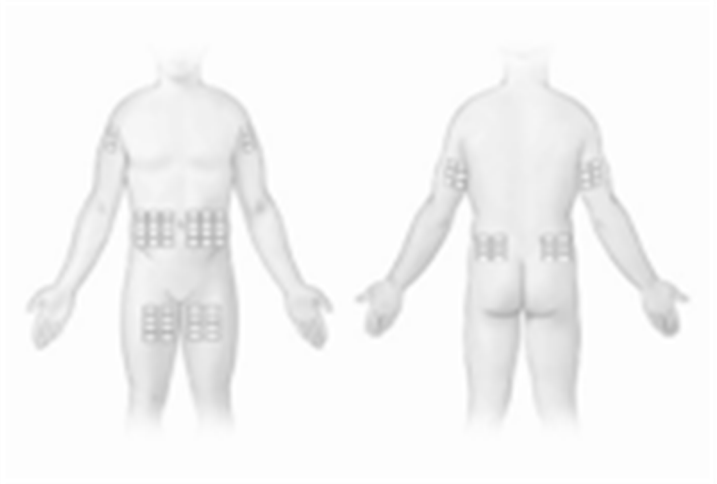

Figure 1: Possible infusion sites for Hizentra

Self-administration at home must be initiated and monitored by a healthcare professional. This healthcare professional must be experienced in caring for patients who are on home treatment. The patient or carer must be instructed and trained in the use of the infusion device, infusion techniques, keeping a treatment diary, recognition of serious adverse reactions, and the measures to be taken should they occur.

Infusion Rate

Hizentra can be infused:

- using an infusion device (e.g., an infusion pump) or
- by manual push with a syringe.

The recommended infusion rate depends on the needs of the individual patient.

<u>Device-assisted infusion</u>

<u>Replacement Therapy</u>

The recommended initial infusion rate should not exceed 20 mL/hour/site. If the infusion is well tolerated, the rate can gradually be increased up to 100 mL/hour/site.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The recommended initial infusion rate should not exceed 20 mL/hour/site. If the infusion is well tolerated, the rate can gradually be increased to 50 mL/hour/site.

For two-weekly dosage regimens, the required volume of Hizentra can be administered in up to 4 sessions, e.g., once in the morning and once in the evening, repeated the following day or within the second week.

Manual push infusion

The recommended initial infusion rate should not exceed 0.5 mL/min/site (30 mL/hour/site).

If the infusion is well tolerated, the rate can gradually be increased to 2.0 mL/min/site. (120 mL/hour/site), based on the healthcare professional's judgement and the tolerability in the individual patient.

A 24-gauge needle or larger (i.e., lower gauge number) is recommended to allow patients higher flow rates with manual push infusions. Using smaller needles (i.e., higher gauge number) may make it more difficult to manually push Hizentra.

Only one infusion site per syringe can be infused.

If a larger volume of >20 mL Hizentra has to be administered by manual push, it is advisable to administer the volume at several sites, depending on the individual dose to be administered. In this case, an additional Hizentra syringe is required for each infusion site. If the volume is infused at several sites, a new sterile injection needle must be used for each infusion syringe.

Administration sets with multiple infusion needles/catheters or sets with bifurcated delivery systems should not be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the listed excipients (see section "Composition").

Hyperprolinaemia type I or II. Hyperprolinaemia is a very rare disease that affects only isolated families worldwide

Hizentra must not be administered intravascularly.

4.4 Warnings and precautions

If Hizentra is inadvertently administered into a blood vessel, patients could go into shock.

The recommended infusion rates given under *Infusion rate* in the section "Dosage/Administration" should be followed. With the first supervised infusions, patients should be closely monitored and carefully observed for any adverse events throughout the infusion and for 20 minutes thereafter.

Certain adverse reactions may occur more frequently in patients receiving human immunoglobulin for the first time or, in rare cases, when switching immunoglobulin products or after a break in treatment of more than eight weeks.

Hypersensitivity/allergic reactions

True hypersensitivity reactions are rare. They may occur in patients with anti-IgA antibodies. Patients with anti-IgA antibodies, in whom subcutaneous IgG products remain the only treatment should be started on Hizentra only under close medical supervision.
Rarely, the administration of human immunoglobulin can induce a sudden drop in blood pressure with an anaphylactic reaction, even in patients who had previously tolerated treatment well.

Possible complications may often be prevented if it is ensured that:

- patients are not hypersensitive to human immunoglobulin, by starting the first infusion of the product at a slow rate (≤ 15 mL/hour/site);
- patients are closely monitored for any symptoms throughout the entire infusion and for at least 20 minutes thereafter. In particular, patients who are receiving human immunoglobulin for the first time, who have been switched from another immunoglobulin product or who have had a prolonged break in treatment should be monitored during the first infusion and for an hour thereafter, in order to detect possible adverse reactions.

The infusion must be stopped immediately if there is any suspicion of an allergic or anaphylactic reaction. In the case of shock, the current standard medical treatment for shock is to be administered.

Embolic and thromboembolic events

There is clinical evidence of a relationship between immunoglobulin administration and embolic/thromboembolic events such as heart attack, stroke, deep vein thrombosis and pulmonary embolism. Special caution should therefore be exercised in patients with pre-existing risk factors for thromboembolic events (such as advanced age, hypertension, diabetes mellitus, a history of vascular disease or thrombotic episodes, congenital or acquired thrombophilic disorders, prolonged periods of immobilisation, severe hypovolaemia, and diseases that increase blood viscosity). Patients should be informed about first symptoms of thromboembolism such as shortness of breath, pain and swelling of

limb, focal neurological deficits and chest pain and should be told to contact their physician immediately at the onset of these symptoms. Patients should be sufficiently well hydrated before the use of immunoglobulins.

Aseptic Meningitis Syndrome (AMS)

Cases of AMS have been reported on treatment with intravenous or subcutaneous immunoglobulin. The syndrome usually begins within a few hours to 2 days after the start of immunoglobulin treatment. AMS is characterised by the following signs and symptoms: severe headache, neck stiffness, drowsiness, fever, photophobia, nausea and vomiting. Patients exhibiting signs and symptoms of AMS should receive a thorough neurological examination, including CSF tests, to rule out other causes of meningitis. Discontinuing immunoglobulin therapy results in remission of AMS within several days without any sequelae.

Renal complications

Cases of severe renal adverse reactions have been reported in patients on immunoglobulin therapy, especially with products containing sucrose (Hizentra does not contain any sucrose). These reactions include acute renal failure, acute renal tubular necrosis, proximal tubulopathy and osmotic nephrosis. Factors that increase the risk of renal complications include pre-existing kidney disease, diabetes mellitus, hypovolaemia, concomitant nephrotoxic medication, age over 65, sepsis, hyperviscosity and paraproteinaemia.

Haemolytic anaemia

Immunoglobulin products may contain blood group antibodies that may act as haemolysins and may cause the immunoglobulins to bin to red blood cells. This may trigger a positive direct antiglobulin reaction (Coombs` test) and rarely haemolysis. A delayed haemolytic anaemia may develop after treatment with immunoglobulins due to the increased sequestration of red blood cells. Haemolytic anaemia has been reported.

Information on viral safety

Hizentra is produced from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include the selection of donors, screening of individual donations and plasma pools for specific infection markers and the inclusion of effective manufacturing steps for the inactivation/elimination of viruses (see section "Properties/Effects"). 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 previously unknown or emerging viruses and other pathogens.

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

Clinical experience shows that there is no transmission of hepatitis A or parvovirus B19 infection with immunoglobulins and it is also assumed that the antibody content makes an important contribution to viral safety.

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

Hizentra contains less than 1 mmol sodium (23 mg) per vial; that is to say essentially “sodium-free”.

4.5 Interactions

Live attenuated virus vaccines

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella and varicella vaccines for a period of at least 6 weeks up to 3 months. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles vaccination, this impairment may persist for up to 1 year. Patients receiving measles vaccine should therefore have their antibody status checked.

4.6 Pregnancy, lactation

There are no data from controlled clinical trials on the use of Hizentra in pregnant women or breastfeeding mothers. Caution should therefore be exercised with use in pregnancy and breast-feeding. However, long-term clinical experience with immunoglobulins indicates that no harmful effects on the course of the pregnancy, the fetus or the neonate are to be expected.

It is important to continue treatment of the pregnant woman to ensure the corresponding passive immunity to the neonate.

Immunoglobulins are excreted in breast milk and may contribute to the transfer of protective antibodies to the neonate.

4.7 Effects on ability to drive and use machines

Certain adverse reactions associated with Hizentra may impair the ability to drive and use machines. Patients who experience adverse reactions during treatment should wait for them to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse drug reactions (ADR) such as chills, headache, fever, vomiting, allergic reactions, nausea, joint paints, low blood pressure and moderate low back pain may occasionally occur with the administration of human immunoglobulin.

Human immunoglobulin may rarely cause hypersensitivity reactions with a sudden drop in blood pressure and, in isolated cases, anaphylactic shock, even in patients who have not shown any hypersensitivity with previous administrations.

Local reactions at the infusion sites: swelling, soreness, redness, induration, local warmth, itching, bruising and rash.

Adverse drug reactions (ADRs) from clinical trials and postmarketing surveillance of Hizentra:

Seven phase III clinical trials on patients with primary immunodeficiency (PID) (n = 231), two phase IV studies on patients with PID (n = 74), one phase III trial on CIDP patients (n = 197) and an extension study on patients with CIDP (n=82) with with Hizentra, (total n = 502) reported the following ADRs, according to the MedDRA System Organ Class and frequency.

The following frequency convention was used: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000). Spontaneous ADRs after the market launch are given as isolated cases.

Infections and infestations

Very common: Nasopharyngitis (19.3%)

Blood and lymphatic system disorders:

Uncommon: Increased blood lactase dehydrogenase

Isolated cases: Haemolytic anaemia**

Immune system disorders:

Uncommon: Hypersensitivity

Isolated cases: Anaphylactic reactions

Nervous system disorders:

Very common: Headache (12.5%)

Common: Dizziness, migraine

Uncommon: Aseptic meningitis syndrome (AMS)*, tremor (including psychomotor hyperactivity)

Isolated cases: Burning sensation, somnolence

Cardiac disorders:

Uncommon: Tachycardia (including increased blood pressure)

Vascular disorders:

Common: Hypertension

Uncommon: Hot flushes, raised aldolase

Isolated cases: Embolic- and thromboembolic events (including thrombosis, embolism, transient ischaemic attacks, hemiparesis, transient loss of vision, haemorrhagic stroke, hemiplegia)

Respiratory, thoracic and mediastinal disorders:

Common: Cough

Gastrointestinal disorders:

Common: Diarrhoea, abdominal pain, nausea, vomiting

Skin and subcutaneous tissue disorders:

Very common: Rash (including erythema) (10.4%)

Common: Pruritus, urticarial, contact dermatitis

Musculoskeletal, connective tissue and bone disorders:

Common: Musculoskeletal pain, arthralgia

Uncommon: Arthritis, muscle spasms, muscle weakness, increased blood creatine phosphokinase

Renal and urinary disorders:

Uncommon: Haematuria, increased creatinine

Isolated cases: Acute renal failure**, acute tubular necrosis**, proximal tubulopathy** und osmotic nephrosis **

General disorders and administration site conditions:

Very common: Infusion site reactions (including contusion and haematomas) (42.2%)

Common: Fatigue (including malaise), pyrexia (including increased body temperature), chest pain, flu-like illness, pain

Uncommon: Chills (including hypothermia), weight loss

Isolated cases: Infusion site ulcer

*Symptoms of AMS include: neck stiffness, headache, pyrexia, photophobia, nausea, and vomiting
**Undesirable class effect of immunoglobulins.

For Information on viral safety, see section "Warnings and precautions".

Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions.

To reports any side effect(s):

- Saudi Arabia:
  The National Pharmacovigilance Centre (NPC):
  SFDA Call Center: 19999
  E-mail: npc.drug@sfda.gov.sa
  Website: https://ade.sfda.gov.sa

- Sultanate of Oman:
  Department of Pharmacovigilance & Drug Information
  Directorate General of Pharmaceutical Affairs & Drug Control
  Ministry of Health, Sultanate of Oman
  Phone Nos. 22357687 / 22357686
  Fax: 22358489
  Email: dg-padc@moh.gov.om
  Website: www.moh.gov.om

- United Arab Emirates:
  Pharmacovigilance & Medical Device section
  P.O.Box: 1853
  Tel: 80011111
  Email: pv@mohap.gov.ae
  Drug Department

Ministry of Health & Prevention
Dubai, UAE

- Other GCC States:
  Please contact the relevant competent authority.

- Algeria:
  http://www.cnpm.org.dz/index.php

- Tunisia :
  effets.indesirables@rns.tn or www.pharmacovigilance.rns.tn

- Jordan:
  Email: jpc@jfda.jo
  JFDA reporting link on JFDA website www.jfda.com:
  https://primaryreporting.who-umc.org/JO
  Tel: +962-6-5632000

4.9 Overdose

The consequences of an overdose are not known.

5. Properties/Effects

ATC code

J06BA01

Pharmacotherapeutic group: immune sera and immunoglobulins: normal human immunoglobulins for extravascular administration.

5.1 Mechanism of action/pharmacodynamics

Hizentra contains a broad spectrum of opsonising and neutralising IgG antibodies against a multitude of bacterial and viral pathogens.

Hizentra contains the IgG antibodies that are present in the general population. It is prepared from plasma from not fewer than 1,000 donors. The IgG subclass distribution corresponds approximately to that of native human plasma.

Adequate doses of Hizentra may restore low IgG antibody levels to the normal range and thus help against infections.

The mechanism of action of Hizentra in patients with CIDP is not fully elucidated but may include immunomodulatory effects.

Clinical efficacy

Primary Immunodeficiency Diseases

The safety and efficacy of Hizentra in the treatment of primary immunodeficiency diseases were evaluated in seven phase III trials and two IV studies in patients with PID.

In the pivotal prospective, multicentre, open-label, single-arm European study, 51 patients aged between 3 and 60 with PID were treated with Hizentra for up to 41 weeks. The mean weekly dose administered was 119 mg/kg body weight. Sustained IgG trough levels with mean concentrations of 7.99 – 8.25 g/L were achieved throughout the entire treatment period. The patients received a total of 1,831 weekly Hizentra infusions.

Forty of the patients (aged 4 - 52) treated in the main trial were enrolled in the subsequent extension study and treated for up to 46 months with the same dosage. The patients received a total of 5,405 weekly Hizentra infusions.
Sustained IgG trough levels with mean concentrations of 7.5 – 8.5 g/L were achieved throughout the treatment period, confirming the findings of the main trial. The rate of acute serious bacterial infections (aSBIs) was 0.0478 per patient per year, with a 99% confidence interval (CI) upper limit of 0.1252.

In the prospective, multicentre, open-label, singe-arm US study, 49 patients aged between 5 and 72 with primary immunodeficiency diseases were treated with Hizentra for up to 15 months. The mean weekly dose administered was 228 mg/kg body weight. Sustained IgG trough levels with a mean concentration of 12.53 g/L were thereby achieved throughout the entire treatment period. The patients received a total of 2,264 weekly Hizentra infusions.

The subsequent US extension study enrolled 21 of the previously treated patients (aged 5 - 69) who continued to be treated at the same dosage for up to 87 weeks. The patients received a total of 1,735 weekly Hizentra infusions.
Sustained IgG trough levels with mean concentrations of 11.71 – 12.76 g/L (overall mean 11.98 g/L) were achieved throughout the entire treatment period, thus confirming the findings of the main trial. None of the patients treated had IgG trough levels below 5 g/L during treatment. The aSBI rate was 0.06 per patient per year, with a 99% confidence interval upper limit of 0.257.

To assess the safety and tolerability of higher infusion rates used with manual push and device-assisted administration, 49 patients with PID, aged from 2 to 75 years, were enrolled in a phase IV, multicentre, non-randomised, open-label study (HiLo) and treated with Hizentra for at least 12 weeks (11 children aged 2 to <18, 35 adults aged 18 to 65, and 3 elderly patients aged >65 years). In the first

patient group, which received Hizentra by the manual push technique (n=16), 2 to 7 infusions per week were administered with infusion rates of 30, 60 und 120 mL/hour/site (see section "Dosage/Administration"). In the second patient group, which received Hizentra with the aid of a pump (n=18), weekly Hizentra infusions were administered with 25, 50, 75 and 100 mL/hour/site flow rates. In the third patient group (n=15), infusion volumes of 25, 40 and 50 mL per site were additionally evaluated in the pump-assisted administration of weekly Hizentra doses (n=15). In all three groups, each infusion parameter was used for 4 weeks. After this time, patients who tolerated the infusions well (responders) could switch to the next higher infusion parameter.
The primary endpoint was the percentage of patients responding to a higher infusion parameter after the switch:

Group	**Infusion parameter and responder* rate (%)**				**Tolerability****
1. Manual push infusion rates	**30 mL/hour** 100.0%	**60 mL/hour** 100.0%	**120 mL/hour** 87.5%	-	1.0
2. Pump-assisted infusion rates	**25 mL/hour** 77.8%	**50 mL/hour** 77.8%	**75 mL/hour** 66.7%	**100 mL/hour** 61.1%	1.0 (0.98–1.0)
3. Pump-assisted infusion volumes	**25 mL** 86.7%	**40 mL** 73.3%	**50 mL** 73.3%	-	1.0

* Responder: in the pump-assisted group, a patient who performed ≥3 valid infusions out of 4 for an infusion parameter; in the manual push group, a patient who performed ≥60% valid infusions for an infusion parameter.
An infusion was considered valid if ≥95% of the planned flow rate/volume per ≥1 infusion site was achieved.
** Tolerability: the number of infusions without serious local reactions divided by the total number of infusions

Overall, the number of infusions without serious local reactions versus the total number of infusions (tolerability) was ≥0.98 in all groups for all infusion parameters.
No clinically relevant differences in the serum IgG trough concentrations were observed between the baseline on Day 1 and the end of the study in all patients.

Safety and efficacy in elderly patients

No overall differences with respect to safety and efficacy were observed between patients with PID over the age of 65 and those aged 18 to 65. In the clinical trials, Hizentra was evaluated in 13 patients with PID who were older than 65.

Safety and efficacy in paediatric patients

The safety and efficacy of Hizentra have been evaluated in paediatric patients aged between 2 and 18 years.

Hizentra was evaluated in 68 paediatric patients with PID aged 2 to <12 years and in 57 paediatric patients who were 12 to <18 years of age.

No differences were found in the pharmacokinetic parameters, safety or efficacy between the paediatric patients and adult subjects.

No specific dose adjustments were necessary to achieve the desired serum IgG levels in the paediatric population.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The safety, efficacy and tolerability of Hizentra in patients with CIDP were evaluated in the PATH [Polyneuropathy and Treatment with Hizentra] study, a phase III, multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. 172 subjects previously treated with IVIg were randomised into groups receiving 0.2 g/kg body weight Hizentra weekly, 0.4 g/kg body weight Hizentra weekly or placebo and then treated for 24 weeks. The mean duration of exposure was 118.9 days in the 0.2 g/kg body weight group and 129 days in the 0.4 g/kg body weight group (maximum exposure in each of the two groups was up to 167 days and 166 days, respectively). Subjects generally used 4 infusion sites at the same time (up to 8 sites simultaneously).

In total, 57 subjects received 1,514 infusions in the placebo group, 57 subjects received 2,007 infusions in the 0.2 g/kg body weight Hizentra group, and 58 subjects received 2,218 infusions in the 0.4 g/kg body weight Hizentra group (total of 5,739 infusions).

The primary efficacy endpoint was the percentage of subjects who had CIDP relapse (defined as a ≥1 point increase in the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score compared with baseline) or were withdrawn during the Hizentra treatment period for any other reason. Both Hizentra doses demonstrated superiority over placebo for the primary endpoint.

A statistically significant smaller percentage of subjects treated with Hizentra had CIDP relapse or was withdrawn from the study for other reasons: 32.8% for 0.4 g/kg body weight and 38.6% for 0.2 g/kg body weight, compared with 63.2% of subjects treated with placebo [$p < 0.001$ and $p = 0.007$, respectively]. Taking relapse alone into consideration, the CIDP relapse rates were 19.0% for 0.4 g/kg body weight Hizentra and 33.3% for 0.2 g/kg body weight Hizentra, compared with 56.1% for placebo

($p < 0.001$ and $p = 0.012$, respectively). Over the treatment period of up to 24 weeks, therefore, Hizentra prevented relapse in 81% and 67% of subjects in the 0.4 g/kg body weight and 0.2 g/kg body weight groups, respectively. In the placebo group, 44% of the subjects did not have a relapse.
The time to CIDP relapse was evaluated, and corresponding probabilities for a CIDP relapse based on Kaplan-Meier estimates were: placebo 58.8%; 0.2 g/kg body weight Hizentra 35.0% and 0.4 g/kg body weight Hizentra 22.4%. The hazard ratios (95% CI) for the lower dose and the higher dose compared with placebo were 0.48 (0.27; 0.85) and 0.25 (0.12; 0.49), respectively. The difference observed between the 0.2 g/kg body weight Hizentra group and the 0.4 g/kg body weight Hizentra group did not reach statistical significance.
With respect to the efficacy result (INCAT score, mean grip strength and the Medical Research Council (MRC) sum score), subjects in both Hizentra dose groups remained stable compared with subjects in the placebo group, whose results deteriorated. Subjects in the high-dose Hizentra group remained stable on Rasch-built Overall Disability Scale (RODS) centile score. The electrophysiology parameters remained stable in subjects in both Hizentra dose groups.

82 patients with CIDP from the PATH study were enrolled in the phase III, multicentre, 48-week, open-label, extension study. The extension study evaluated the long-term safety and efficacy of Hizentra maintenance therapy with two different weekly doses of 0.2 g/kg body weight or 0.4 g/kg body weight. The study design allowed the same patient to receive both doses during the study, 72 patients received a dose of 0.4 g/kg body weight and 73 patients received a dose of 0.2 g/kg. The mean duration of the treatment was 125.8 days (range: 1-330) in the 0.2 g/kg body weight and 196.1 days (range: 1-330) in the 0.4 g/kg body weight group.
Patients who had completed the pivotal PATH study without a relapse on the 0.4 g/kg body weight dose and initially received this dose in the extension study had a relapse rate of 5.6% (1 out of 18 patients).
Of all patients who received 0.4 g/kg body weight dose in the PATH extension study, 9.7% (7 out of 72 patients) had a relapse.
The patients who completed the PATH study without a relapse on the 0.2 g/kg body weight dose and initially received this dose in the extension study had a relapse rate of 50% (3 out of 6 patients).
Of all patients who received the 0.2 g/kg body weight dose in the extension study, 47.9% (35 out of 73 patients) had a relapse. In the extension study, it was possible to reduce the dose from 0.4 g/kg to 0.2 g/kg body weight in 67.9% of the subjects (19 out of 28 patients) without a relapse occurring. All the patients with a relapse recovered within 4 weeks after treatment with 0.4 g/kg body weight.
Grip strength, the MRC sum score, and the RODS centile score remained stable with respect to baseline in patients who did not have a relapse in the extension study.

Safety and efficacy in elderly patients

No overall differences with respect to safety and efficacy were observed between patients over the age of 65 and those aged 18 to 65. In the clinical trials, 61 patients with CIDP who were older than 65 were treated with Hizentra.

Safety and efficacy in paediatric patients

Treatment with Hizentra of paediatric CIDP patients has not been evaluated in clinical studies.

5.2 Pharmacokinetics

Absorption

Following the subcutaneous administration of Hizentra, peak serum IgG levels are achieved after approximately 2 days.

Distribution

Primary Immunodeficiency Diseases

Simulations with population-pharmacokinetic models suggest that comparable IgG exposure (C_{max}, $AUC_{0\text{-}14days}$, $C_{min,\ 14\ days}$) is obtained if double the weekly dose of Hizentra is administered every two weeks. These simulations further show that comparable IgG exposure is achieved if the weekly maintenance dose of Hizentra is administered in divided doses (e.g., twice a week, 3 times a week or 5 times a week or daily).

With a continuous daily dosage regimen, the simulations show that missing 2-3 daily doses results in a mean reduction in serum IgG levels of ≤ 4% compared with continuous daily dosing. When the missed doses are administered in addition to the daily dose on the first day of resuming daily dosing, the mean IgG concentration profile recovers within 2 – 3 days. However, if the missed doses are not replaced when daily dosing is resumed, it takes up to 5-6 weeks´ treatment to obtain similarly high IgG trough levels.

Elderly patients

No overall differences in the pharmacokinetic parameters were observed between patients with PID aged >65 years and those aged 18 to 65.

Children and adolescents

No differences were seen in the pharmacokinetic parameters between adult and paediatric subjects with PID.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

In the PATH study, subjects (n = 172) achieved sustained trough levels over a period of 24 weeks when receiving weekly doses of 0.2 g/kg body weight or 0.4 g/kg body weight. The mean (±SD) IgG-trough concentrations after Hizentra treatment was 20.4 (±3.24) g/L in the 0.4 g/kg body weight group and 15.4 (±3.06) g/L in the 0.2 g/kg body weight group. Simulations with population-pharmacokinetic models in the PATH study suggest that comparable IgG exposure (C_{max}, $AUC_{0\text{-}14\ days}$, $C_{min,\ 14\ days}$) is achieved when the subjects with CIDP are given double the weekly Hizentra dose every two weeks. These simulations further suggest that comparable IgG exposure is also achieved in the CIDP patient population when the weekly maintenance dose of Hizentra is divided into several more frequent doses (2 - 7 times a week).

Children and adolescents

Treatment with Hizentra has not been evaluated in clinical trials on paediatric patients with CIDP who are under the age of 18.

Elderly patients

No overall differences in the pharmacokinetic parameters were observed between patients with CIDP aged >65 and those aged 18 to 65.

Metabolism

Not specified.

Elimination

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

5.3 Preclinical data

Immunoglobulins are a normal constituent of the human body. L-proline is a physiological, non-essential amino acid.

The safety of Hizentra has been tested in several preclinical studies, with special reference to the excipient L-proline. Preclinical data on safety pharmacology and toxicity showed no evidence of a particular risk for human.

6. Pharmaceutical particulars

6.1 List of excipients

Please see section 2 b.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Effects on diagnostic methods

After the infusion of immunoglobulins, the transient rise in the various antibodies passively transferred into the patient's blood may result in false positive serology test results.

The passive transmission of antibodies to erythrocyte antigens, e.g. A, B and D, may interfere with some serological tests for red cell alloantibodies (e.g., Coombs´ test), the reticulocyte count and the haptoglobin tests.

Interactions with live attenuated vaccines: see section “Interactions”.

6.3 Shelf life

Hizentra may be stored until the expiry date indicated by “EXP” on the label and the outer carton. Do not use the product after the expiry date (EXP) printed.

Shelf life after opening:

Hizentra is intended for single use. Because the solution contains no preservative, Hizentra should be used/infused as soon as possible after opening the vial.

6.4 Special precautions for storage

Do not store above 25 C. Do not freeze.

Keep the vial in its original packaging in order to protect the contents from light.

Keep out of the reach of children.

6.5 Nature and contents of container

Pack sizes

1 x 5 ml (1g) vial

1 x 10 ml (2g) vial

1 x 20 ml (4g) vial

1 x 50 ml (10g) vial

Not all pack sizes may be marketed

6.6 Instructions for handling

Hizentra is available as a ready-to-use solution in single-use vials.

The medicinal product should be brought to room or body temperature before use.

The solution should be clear and pale yellow to light brown. Do not use the solution if it is cloudy or contains deposits.

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

7. Marketing authorisation holder and Manufacturer

CSL Behring AG

Wankdorfstrasse 10

3014 Bern

Switzerland

8. Marketing authorisation number

9. Date of first authorisation/ renewal of the authorisation

10. Date of revision of the text

October 2022

Note: Hizentra ® is a registered trademark of CSL Behring AG in many countries.