CSL Behring

Name of the medicinal product

Hizentra 200 mg/ml solution for subcutaneous injection

Composition

a. Active substance

Human normal immunoglobulin for subcutaneous injection (SCIg)

Human plasma protein, of which at least 98% is immunoglobulin type G (IgG).

The approximate distribution of IgG subclasses is as follows: IgG_1 69%, IgG_2 26%, IgG_3 3%, IgG_4 2%.

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

b. Excipients

L-proline, Polysorbate 80, water for injections q.s. to 1 ml.

Pharmaceutical form and active substance content per unit

Solution for subcutaneous injection.

1 ml contains: 200 mg of human plasma protein, of which at least 98% is IgG (20% solution).

The osmolality is approximately 380 mOsmol/kg.

The solution is clear. The colour can vary from pale-yellow to light-brown.

Therapeutic Indications

Replacement therapy in adults and children in primary immunodeficiency syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency and Wiskott-Aldrich syndrome

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

Immunomodulatory therapy:

- Hizentra is indicated for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with intravenously administered immunoglobulins (IVIg).

Posology/Method of administration
The dose and dose regimen are dependent on the indication.

Posology for adults and children
The dose may need to be individualized for each patient dependent on the clinical response and serum IgG trough levels. The following dose regimens are given as a guideline:

Replacement therapy
The dose regimen using the subcutaneous route should achieve a sustained level of IgG. A loading dose of at least 0.2 to 0.5 g/kg (1.0 to 2.5 ml/kg) body weight may be required. This may need to be divided over several days. After steady state IgG levels have been attained, maintenance doses are divided into smaller doses and administered at repeated intervals to reach a cumulative monthly dose in the order of 0.4 to 0.8 g/kg (2.0 to 4.0 ml/kg) body weight (see section "Pharmacokinetics").

For patients switching from intravenous treatment the monthly dose is divided into smaller doses and administered at repeated intervals (see section "Pharmacokinetics").

Trough levels should be measured and assessed in conjunction with the patient's clinical response. Depending on the clinical response (e.g. infection rate), adjustment of the dose and/or the dose interval may be considered in order to aim for higher trough levels.

Immunomodulatory therapy in CIDP patients
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.

Paediatric population

As the posology is given by body weight and adjusted to the clinical outcome of the above mentioned conditions, the dosage regimen is the same in the paediatric population as in adults. Hizentra was evaluated in 68 paediatric subjects with PID, aged 2 to <12 years and in 57 adolescents aged 12 to <18 years. No paediatric-specific dose requriements were necessary to achieve the desired serum IgG levels

Hizentra was not evaluated in clinical studies in paediatric patients with CIDP who are under the age of 18.

Geriatric population

As the dose is given by body weight and adjusted to the clinical outcome of the above mentioned conditions, the dose in the geriatric population is not considered to be different from that in subjects 18 to 65 years of age.

In clinical studies Hizentra was evaluated in 13 subjects with PID >65 years of age and no specific dose adjustments were necessary to achieve the desired serum IgG levels.

In clinical studies Hizentra was evaluated in 61 subjects with CIDP >65 years of age and no specific dose adjustments were necessary to achieve the desired clinical outcome.

Method of administration

Hizentra must be administered via the subcutaneous route only.

Hizentra may be infused into sites such as abdomen, thigh, upper arm, and/ or lateral hip (see Figure 1). If large doses are given (>50ml), it is may be advisable to administer the dose at multiple sites. There is no limit to the number of infusion sites administered in parallel. 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 (2 inches) apart. For subsequent administration, the infusion sites should be changed.

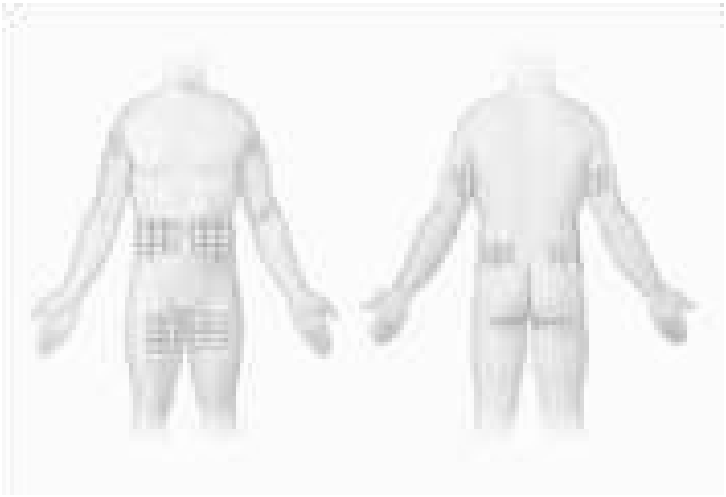


Figure 1: Possible infusion sites for Hizentra

Infusion rate
Hizentra can be infused using:

- an infusion device or
- by manual push with syringe

The recommended initial infusion rate depends on the individual patient's needs.

Device-assisted infusion

The initial infusion rate should not exceed 20 ml / hour / site.

If well-tolerated (see also section "Warning and precautions for use"), the infusion rate can then gradually be increased to 35 ml/hour/site for the subsequent two infusions. Thereafter, the infusion rate can be further increased as per patient`s individual tolerability.

Manual push infusion

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

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

It is recommended to use needles gauge 24 or larger (i.e. lower gauge number). Using smaller needles (i.e. higher gauge number) may hinder manual push of Hizentra. Only one infusion site per syringe can be infused. If administration with an additional Hizentra syringe is required, a new sterile injection needle should be used and the infusion site changed.

Home-treatment

Subcutaneous infusion for home treatment should be commenced and initially monitored by a healthcare professional. The patient or the caregiver will be instructed in the use of infusion devices, infusion techniques, how to keep a treatment diary, and identification of severe adverse reactions and measures to

be taken in case such reactions occur.

For patients at risk, administer Hizentra at the minimum dose and infusion rate practicable (see section "Warnings and precautions for use").

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section "Composition"). Hyperprolinaemia type I and II. This is an extremely rare disorder. Only a few families with this disease are known worldwide.

Warnings and precautions for use

Route of administration

Hizentra is for subcutaneous use only. Hizentra must not be given intravascularly. If Hizentra is accidentally administered into a blood vessel, patients could develop shock.

The recommended infusion rate given under section "Posology/Method of administration: *Infusion rate*" should be adhered to. Patients should be closely monitored during their first supervised infusions with regard to any adverse events during the infusion period and for at least 20 minutes thereafter.

Hypersensitivity / Anaphylaxis

True allergic reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be switched to Hizentra only under close medical supervision.

Rarely, human immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human immunoglobulin.

Certain adverse reactions may occur more frequently in patients who receive human immunoglobulin for the first time or, in rare cases, when the human immunoglobulin product is switched or when treatment has been stopped for more than eight weeks.

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human immunoglobulin, by initially injecting the product slowly (≤ 15 ml/hour/site);
- are carefully monitored for any symptoms throughout the infusion period and for at least 20 minutes after administration. In particular, patients naive to human immunoglobulin, patients switched from

an alternative product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs.

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment should be administered.

Thromboembolism

Arterial and venous thromboembolic events such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Particular caution should be therefore exercised in patients with pre-existing risk factors for thrombotic events such as advanced age, oestrogen use, in-dwelling vascular catheters, history of vascular disease or thrombotic episodes, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, and diseases which increase blood viscosity.

Patients should be informed about first symptoms of thromboembolic events including shortness of breath, chest pain, pain and swelling of limbs, focal neurological deficits and should be advised to contact their physician immediately upon onset of symptoms. Patients should be sufficiently hydrated before use of immunoglobulins.

Aseptic Meningitis Syndrome (AMS)

AMS cases have occurred with use of intravenous or subcutaneous immunoglobulin. The syndrome usually begins within several hours to 2 days following immune globulin 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 studies, to rule out other causes of meningitis. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

Information on safety with respect to transmissible agents

Hizentra is made from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses (see section “Properties/Effects”). Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

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

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

Interactions

Live attenuated virus vaccines

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

Interference with serological testing

After infusion of IgG, the transitory rise of the various passively transferred antibodies in patient's blood may lead to misinterpretation of the results of serological testing. Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D, may interfere with some serological tests for red cell alloantibodies (e.g. Coombs` test), reticulocyte counts and haptoglobin tests.

Fertility, pregnancy and lactation

Pregnancy

Data from prospective clinical trials on the use of Hizentra in pregnant women is limited. Therefore, Hizentra should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus or the neonate are to be expected.

Continued treatment of the pregnant woman is important to ensure that the neonate is born with appropriate passive immunity.

Lactation

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

Fertility

Based on clinical experience with IgG it is suggested that no harmful effects on fertility are to be expected.

Effects on ability to drive and use machines

There is no indication that immunoglobulins adversely affect the ability to drive or to use machines.

Undesirable effects

Summary of the safety profile

In view of the fact that clinical trials are conducted under controlled conditions, adverse drug reaction (ADR) rates observed in the clinical trials of a drug product may not reflect the rates observed in clinical practice.

The Adverse Reactions (ADRs) have been collected in Hizentra clinical trials from 7 Phase III studies with PID (n = 231) ,2 phase IV studies in patients with PID (n=74), 1 phase III study(n = 115) and 1 extension study (n=82) in patients with CIDP (total N = 502).

The ADRs reported in these clinical studies are summarised and categorised according to the MedDRA System Organ Class (SOC) and Preferred Term Level. The frequencies per patient has been evaluated using the following criteria: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1'000 to <1/100), rare (≥1/10'000 to <1/1'000) and Very rare (≥1/100'000 to <1/10'000), For spontaneous post-marketing ADRs, the reporting frequency is categorised as unknown.

Table 1: Adverse Drug Reactions (ADR) Associated with Hizentra Obtained from Clinical Studies and Post-marketing Surveillance, Reporting Rate per Patient

MedDRA System Organ Class	ADR MedDRA Term	ADR frequency category per patient
Infections and infestations	Nasopharyngitis	Very common
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylactic reactions	Unknown
Nervous system disorders	Headache	Very common
	Dizziness, Migraine	Common
	Tremor (including Psychomotor hyperactivity)	Uncommon
	Meningitis aseptic	Uncommon
	Burning sensation	Unknown
Cardiac disorders	Tachycardia	Uncommon
Vascular disorders	Hypertension	Common
	Flushing	Uncommon
	Embolic and thrombotic events	Unknown
Gastrointestinal disorders	Diarrhoea, Abdominal pain, Nausea, Vomiting	Common
Skin and subcutaneous tissue disorders	Rash	Very common
	Pruritus, Urticaria	Common
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Common
	Arthralgia	Common
	Muscle spasm, Muscular weakness	Uncommon
General disorders and administration site conditions	Infusion site reactions	Very common
	Fatigue (including Malaise), Pyrexia,	Common
	Chest pain, Influenza like illness, Pain	Common
	Chills (including Hypothermia)	Uncommon
	Infusion site ulcer	Unknown
Investigations	Blood creatinine increased	Uncommon

Class effects

Infusion site reactions for SCIg.

Pediatric population

Clinical trials with Hizentra showed a similar overall safety profile in pediatric and adult patients with PID.

Hizentra was not evaluated in clinical studies in paediatric patients with CIDP who were under the age of 18.

Geriatric population

Information available from clinical trials showed no difference in safety profile in patients ≥ 65 years of age than in younger patients. Postmarketing experience with Hizentra in patients ≥ 65 years of age shows an overall similar safety profile in this age group as in younger patients.

Reporting of suspected adverse reactions

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

For safety with respect to transmissible agents: see section “Warnings and precautions for use”.

Overdose

Consequences of an overdose are not known.

Properties/Effects

ATC code: J06BA01

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

Hizentra contains IgG with a broad spectrum of antibodies against infectious agents. It has a distribution of IgG subclasses closely proportional to that in native human plasma. The Fc and Fab functions of the IgG molecule are retained.

Hizentra is usually prepared from pooled human plasma from not less than 1’000 donors by a combination of cold ethanol fractionation, octanoic acid fractionation, combined with a filter aid-assisted depth filtration,

and anion exchange chromatography.

Mechanism of action

This medicine supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. In immunodeficiency, adequate doses of Hizentra may restore abnormally low IgG antibody levels to the normal range and thus help against infections.
The mechanism of action in CIDP is not fully understood, but may include immunomodulatory effects.

Pharmacodynamics effects

The safety and efficacy of Hizentra in patients with has been assessed in 7 phase III studies in patients with PID, 2 phase IV studies with PID, and 1 phase III study in patients with CIDP including 1 extension study.

PID

In the European pivotal prospective open label, single arm and multicentre study, a total of 51 subjects with primary immunodeficiency syndromes aged between 3 and 60 years old were treated with Hizentra for up to 41 weeks. The mean dose administered each week was 119 mg/kg body weight. Sustained IgG trough levels with mean concentrations of 7.99 – 8.25 g/l were thereby achieved throughout the treatment period. Subjects received in total 1831 weekly Hizentra infusions.

In the subsequent extension study a total of 40 patients treated previously in the pivotal study (age 4 to 52 years) were enrolled and treated up to 46 months under the same dosing. Patients received a total of 5405 weekly Hizentra infusions.

Over the entire treatment period constant IgG trough levels were achieved with average concentrations of 7.5 to 8.5 g/l, confirming the results of the pivotal study. The rate of acute serious bacterial infections (aSBI) was 0.0478 per patient per year, with an upper 99% confidence interval (CI) of 0.1252.

In the US prospective open label, single arm and multicentre study, a total of 49 subjects with primary immunodeficiency syndromes aged between 5 and 72 years old were treated with Hizentra for up to 15 months. The mean dose administered each week was 228 mg/kg body weight. Sustained IgG trough levels with a mean concentration of 12.53 g/l were thereby achieved throughout the treatment period. Subjects received in total 2264 weekly Hizentra infusions.

In the subsequent US extension study, a total of 21 previously treated patients (aged 5 to 69 years) were enrolled and treated up to 87 weeks at the same dosing. Patients received a total of 1735 weekly Hizentra

infusions.
Over the entire treatment period constant IgG trough levels were achieved with average concentrations of 11.71 to 12.76 g/l (overall average 11.98 g/l), confirming the results of the pivotal study. In none of the patients treated the trough levels have been shown below 5 g/l during the treatment. The aSBI rate was 0.06 per patient per year, with an upper 99% confidence interval of 0.257.

To assess the safety and tolerability of higher infusion rates applied via the manual push and pump-assisted administration technique, 49 PID subjects aged 2 to 75 years were enrolled in an open-label, multicentre, parallel-arm, nonrandomised phase IV study and treated with Hizentra for at least 12 weeks (11 paediatric patients aged 2 to <18, 35 adult patients aged 18 to 65, and 3 geriatric patients aged >65 years). In the patient group (n=16) receiving Hizentra via the manual push technique (manual push flow rate cohort), 2 to 7 infusions per week were administered with the flow rates of 30, 60 and 120 ml/hour/site corresponding to 0.5 ml/min, 1.0 ml/min or 2.0 ml/min per site. In the patient group (n=18) receiving Hizentra via pump-assisted administration (pump-assisted flow rate cohort), weekly Hizentra infusions were administered with 25, 50, 75 and 100 ml/hour/site flow rate. In addition, higher infusion volumes of 25, 40 and 50ml per site (pump-assisted volume cohort) were evaluated in pump-assisted administration of weekly Hizentra doses (n=15). In all three groups, each infusion parameter was used for 4 weeks, after which tolerating subjects could switch to the next higher infusion parameter.

Overall, the tolerability* was ≥ 0.98 for all infusion parameter levels in all cohorts. The percentage of subjects responding to a higher infusion parameter (= responder**) was: in the manual push flow rate cohort 100.0% at the 30 ml/hour and 60 ml/hour, and 87.5% at the 120 ml/hour per site; in the pump-assisted flow rate cohort 77.8% at the 25 ml/hour and the 50 ml/hour, 66.7% at the 75 ml/hour, and 61.1% at the 100 ml/hour per site; in the pump-assisted volume cohort 86.7% at the 25 ml and 73.3% at the 40 ml and 50 ml per site. No clinically relevant differences in the serum IgG trough concentrations were observed between the baseline at day 1 and at the end of the study in all subjects.

*Tolerability: number of infusions without severe local reactions divided by the total number of infusions
**Responder:
Responder: in the pump-assisted group a subject who performed ≥3 valid infusions out of 4 for an infusion parameter; in the manual push group a subject who performed ≥60 % of 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.

Paediatric population
The safety and effectiveness of Hizentra have been established in paediatric subjects 2 to 18 years of age.

Hizentra was evaluated in 68 paediatric subjects with PID 2 to <12 years of age and in 57 paediatric subjects 12 to <18 years of age. There were no differences in the pharmacokinetics, safety and efficacy profiles as compared with adult subjects. No paediatric-specific dose adjustmentswere necessary to achieve the desired serum IgG levels. No differences were seen in the pharmacodynamic properties between adult and paediatric study patients.

Geriatric population

No overall differences in safety or efficacy were observed between PID subjects >65 years and PID subjects 18 to 65 years of age. In the clinical studies Hizentra was evaluated in 13 patients with PID >65 years of age.

CIDP

The safety, efficacy and tolerability of Hizentra in patients with CIDP has been assessed in a multicentre, double-blind, randomised, placebo-controlled, parallel-group phase III PATH [Polyneuropathy and Treatment with Hizentra] study. 172 subjects previously treated with IVIg were randomised to weekly 0.2 g/kg bw Hizentra, weekly 0.4 g/kg bw Hizentra or placebo groups, and followed for a subsequent 24 weeks. The mean duration of exposure was 118.9 days in the 0.2 g/kg bw and 129 days in the 0.4 g/kg bw Hizentra group (maximum exposure up to 167 and 166 days in each group, respectively). Subjects generally used 4 infusion sites in parallel (up to 8 sites in parallel). In total, 57 subjects received 1514 infusions in the placebo group, 57 subjects received 2007 infusions in the 0.2 g/kg bw Hizentra group, and 58 subjects received 2218 infusions in the 0.4 g/kg bw Hizentra group (in total 5739 infusions).

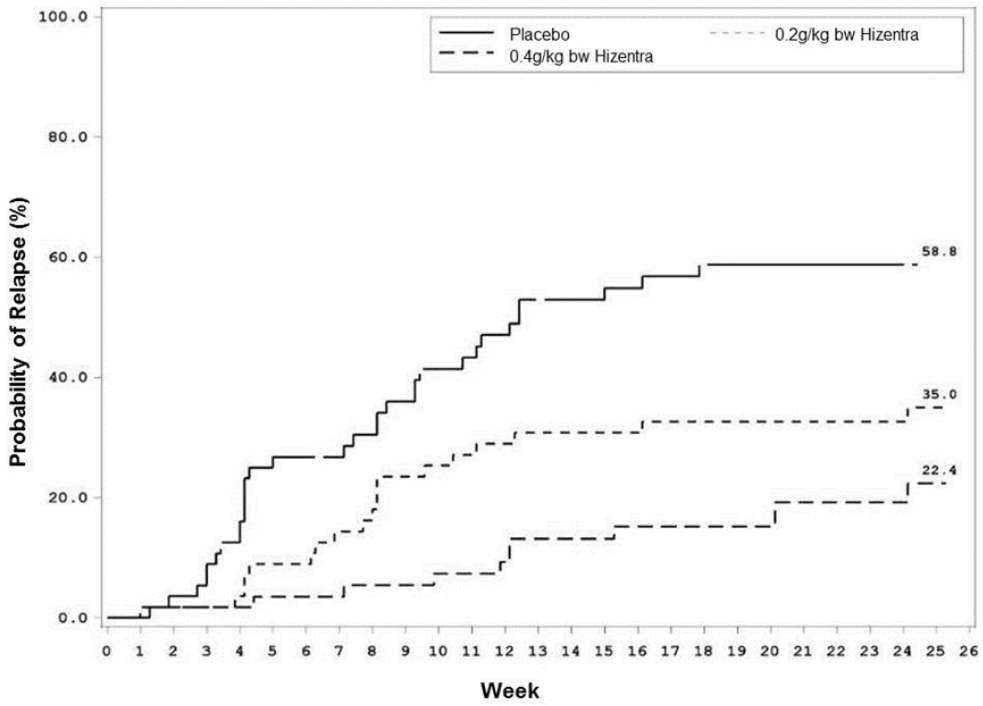
The primary efficacy endpoint was the percentage of subjects who had a CIDP relapse (defined as a ≥ 1 point increase in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] score compared with baseline) or were withdrawn for any other reason in the Hizentra treatment period.

Both Hizentra doses demonstrated superiority over placebo for the primary endpoint. A statistically significant lower percentage of subjects treated with Hizentra, 32.8 % for 0.4 g/kg bw and 38.6 % for 0.2 g/kg bw, had CIDP relapse or was withdrawn for other reasons compared with 63.2 % subjects treated with placebo ($p < 0.001$ or $p = 0.007$, respectively). When only considering relapse, the CIDP relapse rates were 19.0 % for 0.4 g/kg bw Hizentra and 33.3 % for 0.2 g/kg bw Hizentra compared with 56.1 % for placebo ($p < 0.001$ or $p = 0.012$, respectively). Accordingly, over the treatment period for up to 24 weeks Hizentra prevented relapse in 81 % and 67 % of subjects in the 0.4 g/kg bw and 0.2 g/kg bw group, respectively, while in the placebo group 44 % of subjects remained relapse-free.

Time to CIDP relapse (Figure 2) was evaluated, and the corresponding probabilities for CIDP relapse based on Kaplan-Meier estimates were: placebo, 58.8 %; 0.2 /kg bw Hizentra, 35.0 %; and 0.4 g/kg bw Hizentra, 22.4 %. The hazard ratios (95 % CI) for the lower dose and higher dose compared to placebo was 0.48 (0.27, 0.85) and 0.25 (0.12, 0.49), respectively.

The difference observed between the 0.2 g/kg bw and the 0.4 g/kg bw Hizentra groups did not reach statistical significance.

Figure 2. Kaplan-Meier Plot Time to CIDP Relapse



In the efficacy scores (INCAT score, mean grip strength, and Medical Research Council (MRC) sum score), subjects in both Hizentra dose groups remained stable while subjects in the placebo group deteriorated. Subjects in the high dose Hizentra group remained stable in the Rasch-built Overall Disability Scale (R-ODS) centile score. Subjects in both Hizentra dose groups remained stable in electrophysiology parameters.

A phase III, multicentre, 48-week open-label extension study enrolled 82 CIDP patients from the PATH study. The extension study investigated the long-term safety and efficacy of Hizentra maintenance therapy in the two weekly doses, 0.2 g/kg and 0.4 g/kg bw. Due to the study design, the same subject could receive both doses during the study; 72 subjects received doses of 0.4 g/kg and 73 subjects received doses of 0.2 g/kg during the efficacy evaluation period. The mean efficacy evaluation period was 125.8 days (range: 1-330) in the 0.2 g/kg, and 196.1 days (range: 1-330) in the 0.4 g/kg bw group. Patients who completed the pivotal PATH study without relapse on 0.4 g/kg bw dose and initially received this dose in the extension study had a relapse rate of 5.6 % (1/18 patients). For all patients who received 0.4 g/kg bw in the PATH extension study, 9.7 % (7/72 patients) had a relapse. Patients who completed the PATH study without relapse on 0.2 g/kg bw dose and initially received this dose in the extension study had a relapse rate of 50 % (3/6 patients). For all patients who received 0.2 g/kg bw in the extension study, 47.9 % (35/73 patients) had a relapse. Down-titrating patients in the extension study from 0.4 g/kg to 0.2 g/kg bw dose without occurrence

of relapse was possible in 67.9 % of subjects (19/28 patients). All relapsers recovered within 4 weeks after treatment with 0.4 g/kg bw dose. Grip strength, MRC sum score, and R-ODS centile score remained stable as compared to baseline for patients who never had a relapse in the extension study.

Paediatric population

Hizentra was not evaluated in clinical studies in paediatric patients with CIDP who were under the age of 18.

Geriatric population

No overall differences in safety or efficacy were observed between CIDP subjects >65 years of age and subjects 18 to 65 years of age. In the clinical studies with CIDP patients, 61 subjects >65 years of age were treated with Hizentra.

Pharmacokinetics

Absorption and Distribution

Following subcutaneous administration of Hizentra, peak serum levels are achieved after approximately 2 to 3 days. The serum concentrations of total serum IgG, IgG subclasses, and specific IgGs are stable throughout the dosing interval.

Elimination

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

PID

In a clinical phase III trial with Hizentra (n = 46), the subjects achieved sustained trough levels (median 8.1 g / l) over a period of 29 weeks when receiving median weekly doses of 0.06 to 0.24 g / kg bw. Simulations with population-pharmacokinetic models suggested that a comparable IgG exposure (C_{max}, $AUC_{0\text{-}14days}$, $C_{min,\ 14\ days}$) is achieved when the double weekly Hizentra dose is administered every two weeks.

These simulations further suggested that a comparable IgG exposure is achieved when the weekly maintenance dose of Hizentra is divided in several doses (e.g. 2 times per week, 3 times per week, 5 times per week or daily).

If 2-3 daily doses were missed at continuous daily dosing, this resulted in simulations in a median serum IgG level decrease of about ≤ 4% compared to consistent daily dosing. By subsequent administration of the missed doses at the first day in addition to the daily dose, when daily dosing is resumed, the median

concentration profile recovers within 2 to 3 days. However, if missed doses are not replaced when daily dosing is resumed, the steady-state IgG trough levels can be first achieved after a treatment time of up to 5-6 weeks.

Paediatric population
No differences were seen in the pharmacokinetic parameters between adult and paediatric PID study patients.

Geriatric population
No overall differences in the pharmacokinetic parameters were observed between PID subjects >65 years and subjects 18 to 65 years of age.

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 bw and 0.4 g/kg bw, respectively. The mean (SD) IgG trough concentration after Hizentra treatment in the 0.4 g/kg bw group was 20.4 (3.24) g/l and 15.4 (3.06) g/l in the 0.2 g/kg bw group. Simulations with population-pharmacokinetic models in the PATH study suggest that a comparable IgG exposure (C_{max}, $AUC_{0\text{-}14days}$, $C_{min,\ 14\ days}$) is achieved when the double weekly Hizentra dose is administered every two weeks in the CIDP subjects. These simulations further suggest that a comparable IgG exposure is correspondingly achieved when the weekly maintenance dose of Hizentra is divided in several, more frequent doses (2 to 7 times per week) in the CIDP patients` population.

Paediatric population
Hizentra was not evaluated in clinical studies in paediatric patients with CIDP who were under the age of 18.

Geriatric population
No overall differences in the pharmacokinetic parameters were observed between CIDP subjects >65 years and subjects 18 to 65 years of age.

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 assessed in several preclinical studies, with particular reference to the excipient L-proline. Non-clinical data reveal no special risk for humans based on safety pharmacology

and toxicity studies.

Other information

Incompatibilities

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

Shelf life and special precautions for storage

Hizentra can be stored until the expiry date which is stated on the outer carton and the vial label after EXP. Do not use the medicinal product after the expiry date (EXP).

Do not store above 25 °C. Do not freeze.

Keep out of the reach and sight of children.

Keep the vial in the outer carton in order to protect from light.

Shelf life after opening the package:

Hizentra is intended for single-use only. Because the solution contains no preservative, Hizentra should be administered as soon as possible after opening the vial.

Special precautions for handling

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

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

The solution should be clear and pale-yellow or light-brown. Do not use if the solution is cloudy or has particulate matter.

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

Pack sizes

5 ml (1 g), 10 ml (2 g), 20 ml (4 g) and 50 ml (10 g) of solution in a vial.

Manufactured by:

CSL Behring AG

Bern, Switzerland

Date of revision of the text

July 2022

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

Instructions for use

<table>
<tr><td colspan="2">Follow the steps below and use aseptic technique to administer Hizentra.</td></tr>
<tr><td>1</td><td>Clean surface
Thoroughly clean a table or other flat surface using an antiseptic wipe.</td></tr>
<tr><td>2</td><td>Assemble supplies
Place Hizentra and other supplies and equipment needed for the infusion on a clean, flat surface.</td></tr>
<tr><td>3</td><td>Thoroughly wash and dry hands</td></tr>
<tr><td>4</td><td>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.</td></tr>
<tr><td>5</td><td>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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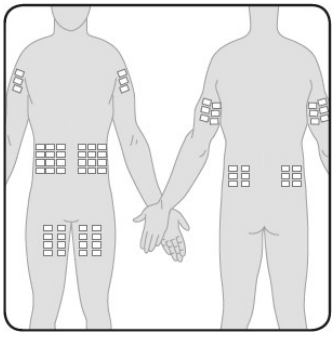
<tr><td>6</td><td>Prepare the tubing
Attach the administration tubing or needle set to the syringe. Prime the tubing to eliminate all remaining air.</td></tr>
<tr><td>7</td><td>Prepare infusion site(s)
Select the infusion site(s) – The number and location of injection sites depends on the volume of the total dose. Each infusion site should be at least 5 cm apart.
You may use an unlimited number of sites simultaneously.

Clean the infuson site(s) using an antiseptic skin preparation, Allow each site to dry before proceeding.</td></tr>
</table>

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 profession.