1. NAME OF THE MEDICINAL PRODUCT

Hizentra Solution for Subcutaneous Injection 200g/L

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (SCIg)

One ml contains:
Human normal immunoglobulin ..... 200 mg
(purity: at least 98% is immunoglobulin type G (IgG))

Vials
Each vial of 5 ml solution contains: 1 g of human normal immunoglobulin
Each vial of 10 ml solution contains: 2 g of human normal immunoglobulin
Each vial of 20 ml solution contains: 4 g of human normal immunoglobulin
Each vial of 50 ml solution contains: 10 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
IgG1.....69%
IgG2.....26%
IgG3.....3%
IgG4.....2%

The maximum IgA content is 50 micrograms/ml.

Produced from the plasma of human donors.

Excipients with known effects
Hizentra contains approximately 250 mmol/L (range: 210 to 290) of L-proline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for subcutaneous injection.
The solution is clear and pale-yellow or light-brown.
Hizentra has an approximate osmolality of 380 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 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
- IgG subclass deficiencies with recurrent infections

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

Immunomodulatory therapy in adults:
– Hizentra is indicated for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with IVIg.

4.2 Posology and method of administration

The dose and dose regimen are dependent on the indication.

Therapy should be initiated and monitored under the supervision of a healthcare professional experienced in the treatment of immunodeficiency/CIDP with SCIg.

Posology
Adults and children

The medicinal product should be administered via the subcutaneous route.

In replacement therapy the dose may need to be individualised for each patient dependent on the clinical response and serum IgG trough levels. The following dose regimens are given as a guideline.

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 of the order of 0.4 to 0.8 g/kg (2.0 to 4.0 ml/kg) body weight. Each single dose may need to be injected at different anatomic sites.

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

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
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 body weight per week administered in 1 or 2 sessions over 1 or 2 consecutive days. The initial subcutaneous dose may be a 1:1 conversion from the previous IVIG dose (calculated as weekly dose).
Example a 1g/kg IVIG dose given every 3 weeks would convert into a 0.33g/kg weekly Hizentra dose. 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. In case of clinical deterioration the dose may be increased to the recommended maximum of 0.4g/kg weekly dose.
Hizentra maintenance therapy in CIDP has not been studied for periods longer than 18 months. Individualize the duration of any treatment beyond 18 months based upon the patient’s response and demonstrated need for continued therapy.

Efficacy of Hizentra has been demonstrated over placebo after switching from intravenous immunoglobulins (IVIG). Direct comparative data for Hizentra versus IVIG are not available. Please refer also to section 5.1.

Paediatric population

The posology in children and adolescents is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome in replacement therapy indications.

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 requirements were necessary to achieve the desired serum IgG levels. Hizentra has not been evaluated in clinical studies in paediatric patients with CIDP who are under the age of 18.

Elderly population
As the dose is given by body weight and adjusted to the clinical outcome of the above mentioned conditions, the dose in the elderly 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

For subcutaneous use only.

Home-treatment
Subcutaneous infusion for home treatment must be initiated and monitored by a healthcare professional experienced in the guidance of patients for home treatment. Infusion devices appropriate for subcutaneous administration of immunoglobulins can be used. The patient or a caregiver must be instructed in the use of infusion devices, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

Hizentra may be infused into sites such as abdomen, thigh, upper arm, and / or lateral hip.
More than one infusion device can be used simultaneously. The amount of product infused into a particular site may vary. In infants and children, infusion site may be changed every 5-15 ml. In adults doses may be given up to 50 ml/site. There is no limit to the number of infusion sites. Infusion sites should be at least 5 cm apart.

Infusion rate
Hizentra can be infused using:

- an infusion device, or
- by manual push with a 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 4.4), the infusion rate can then gradually be increased to 35 ml/hour/site for the subsequent two infusions. Thereafter, if the patient tolerates the initial infusions at the full dose per site and maximum rate, an increase in the infusion rate of successive infusions may be considered at the discretion of the patient and based on the healthcare professionals' judgement

Manual push infusion

The recommended initial infusion rate should not exceed 0.5 ml/min/site (30 ml/hour/site).
If well-tolerated (see also section 4.4), the infusion rate can be increased up to 2.0 ml/min/site (120 ml/hour/site). Thereafter, if the patient tolerates the initial infusions at the full dose per site and maximum rate, an increase in the infusion rate of successive infusions may be considered at the discretion of the patient and based on the healthcare professionals' judgement

A 24 or larger (i.e. lower gauge number) needle gauge may be required to allow patients to infuse at higher flow rates. 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 administration with an additional Hizentra syringe is required, a new sterile injection needle should be used and the infusion site changed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).
Patients with hyperprolinaemia type I or II.
Hizentra must not be given intravascularly.

4.4 Special warnings and precautions for use

Hizentra is for subcutaneous use only. If Hizentra is accidentally administered into a blood vessel, patients could develop shock.

The recommended infusion rate given under section 4.2 should be adhered to. Patients should be closely monitored and carefully observed for any adverse events throughout the infusion period.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal 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 normal immunoglobulin, by initially injecting the product slowly (see section 4.2);
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human normal 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 reactions.

All other patients should be observed for at least 20 minutes after administration.

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

<u>Hypersensitivity</u>
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 normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

<u>Thromboembolism</u>
Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Caution

should be exercised in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity). Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms. Patients should be sufficiently hydrated before use of immunoglobulins.

The drug product should be administered at the minimum dose available and at the minimum rate of infusion practicable. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity assessed.

Aseptic Meningitis Syndrome (AMS)
AMS has been reported with use of IVIg or SCIg. 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
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. 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 strongly 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.

Sodium content
Hizentra is essentially sodium free.

Paediatric population
The same warnings and precautions apply to the paediatric population.

Elderly population
The same warnings and precautions apply to the elderly population.

4.5 Interactions with other medicinal products and other forms of interaction

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 immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (Coombs' test).

Paediatric population
The same interactions may occur in the paediatric population.

Elderly population
The same interactions may occur in the elderly population.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data from prospective clinical trials on the use of human normal immunoglobulin in pregnant women is limited. Therefore, Hizentra should only be given with caution to pregnant women. 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 ensures a passive immunity for the neonate.

Breast-feeding
Data from prospective clinical trials on the use of human normal immunoglobulin in breast feeding women is limited. Therefore, Hizentra should only be given with caution to breast-feeding mothers. Clinical experience with immunoglobulins suggests however that no harmful effects on the neonate are to be expected. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Fertility
Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile
Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

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

For safety with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions

Adverse Reactions (ARs) have been collected in Hizentra clinical trials from 7 phase III studies in patients with primary immunodeficiency (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 patients; 26,646 infusions). The ADRs reported in these clinical studies are summarised and categorised accordingto the MedDRA System Organ Class (SOC and Preferred Term level) and frequency below.

Frequency per patient or per infusionhas 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),Very rare (<1/10,000). For spontaneous post-marketing ADRs, the reporting frequency is categorised as unknown.

Frequency of Adverse Drug Reactions (ADR) associated with Hizentra obtained from clinical studies and post-marketing surveillance, reporting rate per patient or per infusion

System OrganClass (SOC, MedDRA)	**ADRs** (MedDRA Preferred Term, PT)	ADR frequency category per patient	ADR frequency category per infusion
Immune system disorders	Hypersensitivity	Uncommon	Rare
	Anaphylactic reaction	Unknown	Unknown
Nervous system disorders	Headache	Very common	Uncommon
	Dizziness, Migraine	Common	Rare
	Tremor (including Psychomotor hyperactivity)	Uncommon	Rare
	Meningitis aseptic	Uncommon	Very rare
	Burning sensation	Unknown	Unknown
Cardiac disorders	Tachycardia	Uncommon	Very rare
Vascular disorders	Hypertension	Common	Rare
	Flushing	Uncommon	Rare
	Embolic and thrombotic events	Unknown	Unknown
Gastrointestinal disorders	Diarrhoea, Abdominal pain,	Common	Uncommon
	Nausea, Vomitting	Common	Rare
Skin and subcutaneous tissue disorders	Rash	Very common	Uncommon
	Pruritus, Urticaria	Common	Rare
Musculoskeletal and connective tissue disorders	Musculoskeletal pain , Arthralgia	Common	Uncommon
	Muscle spasm, Muscular weakness	Uncommon	Rare
General disorders and administration site conditions	Infusion site reaction	Very common	Very common
General disorders and administration site conditions	Fatigue (including Malaise), Pyrexia	Common	Uncommon
	Chest pain, Influenza like illness, Pain	Common	Rare
	Chills (including Hypothermia)	Uncommon	Rare

	Infusion site ulcer	Unknown	Unknown
Investigations	Blood creatinine increased	Uncommon	Rare

Paediatric population
Clinical trials with Hizentra showed a similar overall safety profile in paediatric and adult patients with PID.
Hizentra was not evaluated in clinical studies in paediatric patients with CIDP who were under the age of 18.

Elderly population
The same adverse reactions may occur in the elderly population. Information available fromclinical trials showed no difference in the safety profile of patients ≥ 65 years of age than of 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.
Please refer to section 4.4 for details on risk factors and monitoring recommendations.

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.

4.9 Overdose

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration, ATC code: J06BA01.

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.
Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1,000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma.

Mechanism of action
In immunodeficiency, adequate doses of Hizentra may restore abnormally low immunoglobulin G antibody levels to the normal range and thus help against infections.
The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

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 0.12 g/kg body weight (bw). Sustained IgG trough levels with mean concentrations of 7.99 – 8.25 g/l were thereby achieved throughout the treatment period. Subjects received in total1,831 weekly Hizentra infusions.

In the US prospective open label, single arm and multicentre study, a total of 49 subjects with primary immunodeficiency syndromes aged between 5 and72 years old were treated with Hizentra for up to 15 months. The mean dose administered each week was 0.23 g/kg bw. Sustained IgG trough levels with a

mean concentration of 12.53 g/l were thereby achieved throughout the treatment period. Subjects received in total 2,264 weekly Hizentra infusions. No serious bacterial infections were reported during the efficacy period in subjects receiving Hizentraduring clinical studies.

To assess the safety and tolerability of higher infusion rates applied via the manual push and pump-assisted administration, 49 PID subjects aged 2 to 75 years were enrolled in an open-label, multicentre, parallel-arm, nonrandomised phase IV HILO (Hizentra Label Optimization) 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 first patient group receiving Hizentra via the manual push technique (n=16), 2 to 7 infusions per week were administered with the flow rates of 30, 60 and 120 ml/hour/site (see section 4.2). In the second patient group receiving Hizentra via pump-assisted administration (n=18), weekly Hizentra infusions were administered with 25, 50, 75 and 100 ml/hour/site flow rate. In a third group, infusion volumes of 25, 40 and 50ml per site were additionally 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 subjects successfully completing required minimal number of valid infusions could switch to the next higher infusion parameter.
The primary endpoint was the percentage of subjects responding to a higher infusion parameter:

Group	**Infusion parameter and responder rate (%)**			
1. manual push flow rates	**30 ml/hour/site**	**60 ml/hour/site**	**120 ml/hour/site**	-
	100.0 %	100.0 %	87.5 %	-
2. pump-assisted flow rates	**25 ml/hour/site**	**50 ml/hour/site**	**75 ml/hour/site**	**100 ml/hour/site**
	77.8 %	77.8 %	66.7 %	61.1 %
3. pump-assisted volumes	**25 ml/site**	**40 ml/site**	**50 ml/site**	-
	86.7 %	73.3 %	73.3 %	-

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.

Overall, the number of infusions without severe 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 at day 1 and the end of the study in all subjects.

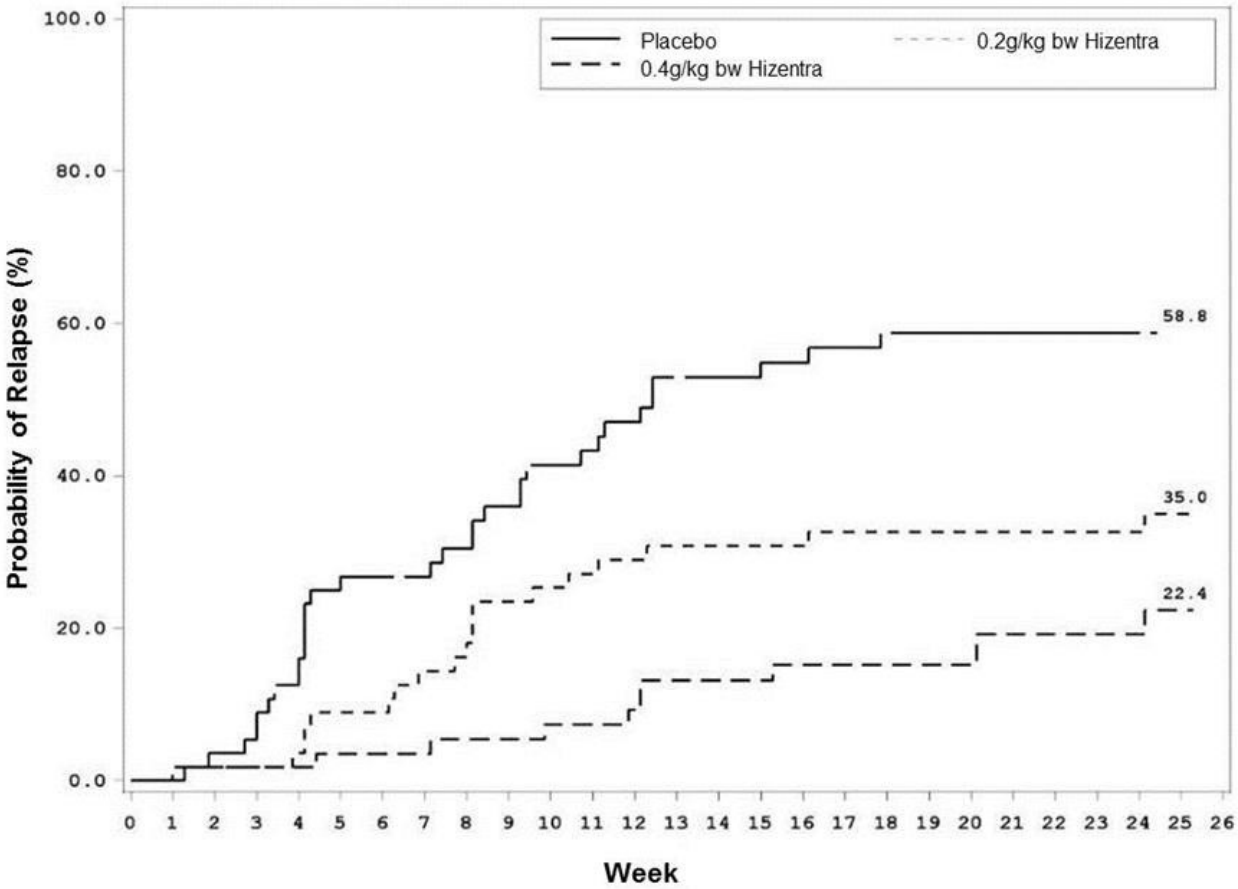
CIDP
The safety, efficacy and tolerability of Hizentra in patients with CIDP has been assessed in a multicentre, double-blind, randomized, placebo-controlled, parallel-group phase III PATH [Polyneuropathy and Treatment with Hizentra] study. 172 adults with definite or probable CIDP who were previously treated with and responded to IVIg were randomized 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 1) 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 1. Kaplan-Meier Plot Time to CIDP Relapse



In the efficacy scores (INCAT score, mean grip strength, and Medical Research Council 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 inthe 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 who completed the PATH study on either dose from 0.4 g/kg to 0.2 g/kg bw dose was possible in 67.9 % of subjects (19/28 patients) without occurrence of relapse; all of

the 9 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
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 adjustments were necessary to achieve the desired serum IgG levels. No differences were seen in the pharmacodynamicproperties between adult and paediatric study patients with PID.
Hizentra has not been evaluated in clinical studies in paediatric patients with CIDP who are under the age of 18.

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

5.2 Pharmacokinetic properties

Absorption and Distribution
Following subcutaneous administration of Hizentra, peak serum levels are achieved after approximately 2 days.

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/kgbw.

Simulations by empirical Population Pharmacokinetic models suggested that comparable IgG exposurelevels ($AUC_{0\text{-}14days}$, $C_{min\ 14days}$) may be obtained if Hizentra is administered subcutaneously every twoweeks using double the weekly dose during maintenance therapy.
These simulations further suggested that comparable serum IgG trough levels can be achieved when the weekly maintenance dose of Hizentra is administered in proportional amounts more frequently than once a week (e.g. 2 times per week, 3 times per week, 5 times per week or daily).

Simulation of 2-3 missed daily doses resulted in a median serum IgG level decrease of ≤ 4% compared to consistent daily dosing. By replacing the missed doses when daily dosing was resumed, the median concentration profile recovered within 2 to 3 days. However, if missed doses were not replaced when dosing was resumed, it took up to 5-6 weeks for the IgG trough levels to return to steady-state.

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

Elderly 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 (Cmax, AUC0-14days, Cmin, 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 has not been evaluated in clinical studies in paediatric patients with CIDP who are under the age of 18.

Elderly population

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

5.3 Preclinical safety 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-proline
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months
Once a vial has been opened, the solution should be used immediately.

6.4 Special precautions for storage

Do not use Hizentra 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.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vials
5, 10 or 20 ml of solution in a vial (type I glass) and 50 ml of solution in a vial (type II glass), with a stopper (halobutyl), a cap (aluminium crimp) and a flip off disc (plastic).

Pack sizes:
1 g / 5 ml
2 g / 10 ml
4 g / 20 ml
10 g / 50 ml

Alcohol swabs, needles and other supplies or equipment are not contained in the pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Hizentra comes as a ready-to-use solution in single-use vials. Because the solution contains no preservative, Hizentra should be used/infused as soon as possible after opening the vial.

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

The solution should be clear and pale-yellow or light-brown.
Solutions that are cloudy or have deposits should not be used.

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

7. MANUFACTURED BY:

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8. DATE OF REVISION OF THE TEXT

Oct 2021