ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hizentra 200 mg/ml solution for subcutaneous injection
Hizentra 200 mg/ml solution for subcutaneous injection in pre-filled syringe

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

Pre-filled syringes
Each pre-filled syringe of 5 ml solution contains: 1 g human normal immunoglobulin
Each pre-filled syringe of 10 ml solution contains: 2 g human normal immunoglobulin
Each pre-filled syringe of 20 ml solution contains: 4 g human normal immunoglobulin
Each pre-filled syringe of 50 ml solution contains: 10 g 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, children and adolescents (0-18 years) in:
– Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).

– Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l.

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

Immunomodulatory therapy in adults, children and adolescents (0-18 years):
– 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 (0-18 years)

Replacement therapy
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 should achieve a trough IgG level (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. 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 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.

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 1 g/kg IVIG dose given every 3 weeks would convert into a 0.33 g/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 0.4 g/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 (0-18 years) 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
As the dose is given by body weight and adjusted to the clinical outcome of the above mentioned conditions, the dose in elderly 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. The healthcare professional must select the appropriate way of infusion (device-assisted or manual push infusion), based on patient`s individual medical situation and preferences. Infusion devices appropriate for subcutaneous administration of immunoglobulins can be used. The patient or a caregiver must be instructed and trained 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.

If a Hizentra pre-filled syringe is used for the administration by manual push, use of 5 ml, 10 ml or 20 ml pre-filled syringe presentation is recommended.

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

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

Hypersensitivity
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 treated with 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.

Thromboembolism
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.

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.

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).

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per vial/syringe, that is to say essentially 'sodium-free'.

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

Elderly
The same warnings and precautions apply to the elderly.

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.

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

Elderly
The same interactions may occur in the elderly.

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

Hizentra has minor influence on the ability to drive and use machines, e.g. dizziness (see section 4.8). Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating 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 according to the MedDRA System Organ Class (SOC and Preferred Term level) and frequency below.

Frequency per patient or per infusion 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), Very rare (<1/10,000). For spontaneous post-marketing ADRs, the reporting frequency is categorised as unknown.
Within each frequency grouping, the adverse reactions are presented in the order of decreasing frequency.

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 Organ Class (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, Vomiting	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
	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
The same adverse reactions may occur in the elderly. Information available from clinical 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 via the national reporting system listed in Appendix V.

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 total 1,831 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 and 72 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 Hizentra during 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 50 ml 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

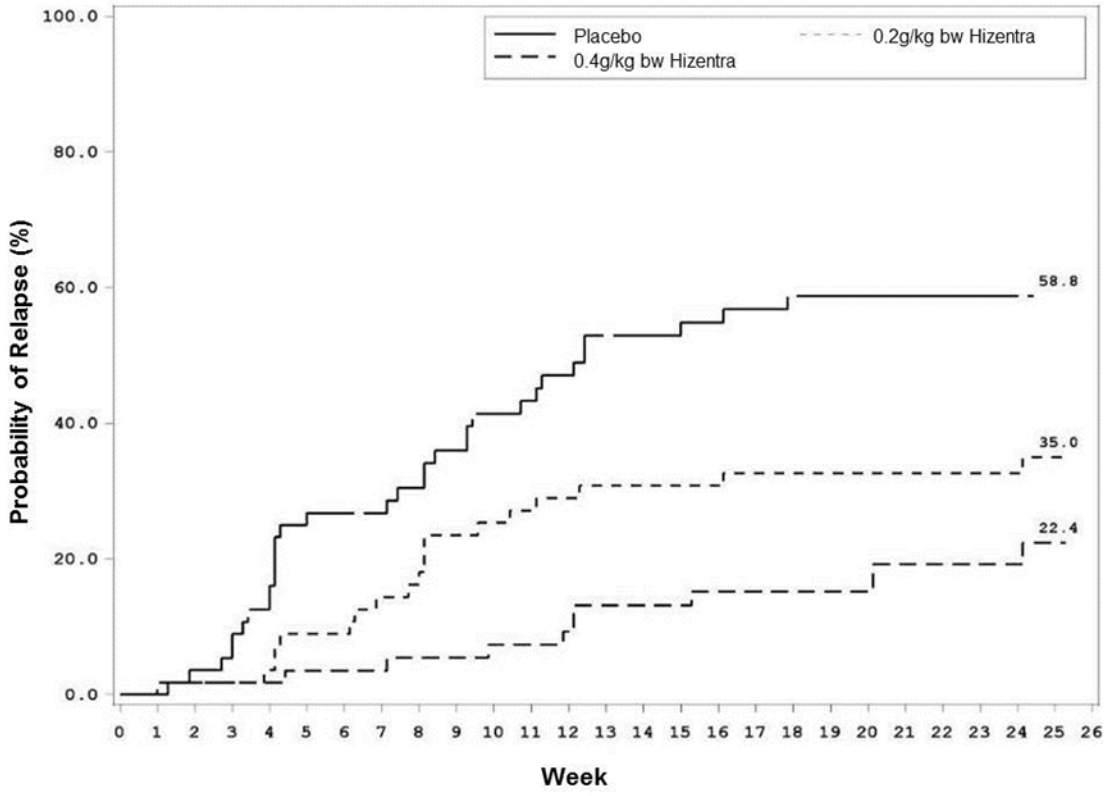
The safety, efficacy and tolerability of Hizentra in patients with CIDP has been assessed in a multicentre, double-blind, randomised, placebo-controlled, parallel-group phase III PATH [Polyneuropathy and Treatment with Hizentra] study. 172 adults with definite or probable CIDP who were previously treated with and responded to IVIg were 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 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 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 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 pharmacodynamic properties 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
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/kg bw.

Simulations by empirical Population Pharmacokinetic models suggested that comparable IgG exposure levels ($AUC_{0\text{-}14days}$, $C_{min,\ 14days}$) may be obtained if Hizentra is administered subcutaneously every two weeks 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
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, $AUC_{0\text{-}14days}$, $C_{min,\ 14\ days}$) 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 has not been evaluated in clinical studies in paediatric patients with CIDP who are under the age of 18.

Elderly
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
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH adjustment)

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 or the blistered pre-filled syringe has been opened, the solution should be used immediately.

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.
Keep the vial or the blistered pre-filled syringe in the outer carton in order to protect from light.

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 of 1, 10 or 20 vials:
1 g / 5 ml
2 g / 10 ml
4 g / 20 ml
10 g / 50 ml

Pre-filled syringes
5, 10, 20 or 50 ml of solution in a pre-filled syringe (cyclo-olefin-copolymer (COC)) blistered with an oxygen absorber pack.

Pack sizes of 1 pre-filled syringe:
1 g / 5 ml
2 g / 10 ml
4 g / 20 ml
10 g / 50 ml

Pack sizes of 10 pre-filled syringes:
1 g / 5 ml
2 g / 10 ml
4 g / 20 ml
10 g / 50 ml

Pack sizes of 20 pre-filled syringes:
2 g / 10 ml
4 g / 20 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 or single-use pre-filled syringes. Hizentra should be used/infused as soon as possible after opening the vial or blistered pre-filled syringe. Do not use Hizentra if the vial or blistered pre-filled syringe is open or defective.

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, waste material and the oxygen absorber pack should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

8. MARKETING AUTHORISATION NUMBERS

Vials
EU/1/11/687/001
EU/1/11/687/002
EU/1/11/687/003
EU/1/11/687/004
EU/1/11/687/005
EU/1/11/687/006
EU/1/11/687/010
EU/1/11/687/011
EU/1/11/687/012
EU/1/11/687/013
EU/1/11/687/014

Pre-filled syringes
EU/1/11/687/015
EU/1/11/687/016
EU/1/11/687/017
EU/1/11/687/018
EU/1/11/687/019
EU/1/11/687/020
EU/1/11/687/021
EU/1/11/687/022
EU/1/11/687/023
EU/1/11/687/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 April 2011
Date of first renewal: 18 February 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

CSL Behring AG
Wankdorfstrasse 10
CH-3000 Bern 22
Switzerland

or

CSL Behring (Australia) Pty Ltd
189-209 Camp Road
Broadmeadows, Vic 3047, Australia

Name and address of the manufacturer responsible for batch release

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX (vial)

1. NAME OF THE MEDICINAL PRODUCT

Hizentra 200 mg/ml solution for subcutaneous injection
human normal immunoglobulin (SCIg)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Human normal immunoglobulin 200 mg
IgG..... ≥ 98%
IgA.....≤ 50 micrograms

1 g/5 ml
2 g/10 ml
4 g/20 ml
10 g/50 ml

3. LIST OF EXCIPIENTS

Excipients: L-proline, polysorbate 80, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 5 ml
1 x 10 ml
1 x 20 ml
1 x 50 ml
10 x 5 ml
10 x 10 ml
10 x 20 ml
10 x 50 ml
20 x 5 ml
20 x 10 ml
20 x 20 ml

Vial(s)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not inject intravascularly.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
D-35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/687/001 1 x 5 ml vial
EU/1/11/687/002 10 x 5 ml vials
EU/1/11/687/003 20 x 5 ml vials
EU/1/11/687/004 1 x 10 ml vial
EU/1/11/687/005 10 x 10 ml vials
EU/1/11/687/006 20 x 10 ml vials
EU/1/11/687/010 1 x 20 ml vial
EU/1/11/687/011 10 x 20 ml vials
EU/1/11/687/012 20 x 20 ml vials
EU/1/11/687/013 1 x 50 ml vial

EU/1/11/687/014 10 x 50 ml vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hizentra
1 g
2 g
4 g
10 g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX (pre-filled syringe)

1. NAME OF THE MEDICINAL PRODUCT

Hizentra 200 mg/ml solution for subcutaneous injection in pre-filled syringe
human normal immunoglobulin (SCIg)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Human normal immunoglobulin 200 mg
IgG..... ≥ 98%
IgA.....≤ 50 micrograms

1 g/5 ml
2 g/10 ml
4 g/20 ml
10 g/50 ml

3. LIST OF EXCIPIENTS

Excipients: L-proline, polysorbate 80, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 5 ml
1 x 10 ml
1x 20 ml
1 x 50 ml
10 x 5 ml
10 x 10 ml
10 x 20 ml
10 x 50 ml
20 x 10 ml
20 x 20 ml

Pre-filled syringe(s)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not inject intravascularly.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Do not freeze.
Keep the blistered pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
D-35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/687/015 1 x 5 ml pre-filled syringe
EU/1/11/687/016 10 x 5 ml pre-filled syringes
EU/1/11/687/017 1 x 10 ml pre-filled syringe
EU/1/11/687/018 10 x 10 ml pre-filled syringes
EU/1/11/687/019 1 x 20 ml pre-filled syringe
EU/1/11/687/020 10 x 20 ml pre-filled syringes
EU/1/11/687/021 20 x 10 ml pre-filled syringes
EU/1/11/687/022 20 x 20 ml pre-filled syringes
EU/1/11/687/023 1 x 50 ml pre-filled syringe
EU/1/11/687/024 10 x 50 ml pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hizentra
1 g
2 g
4 g
10 g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hizentra 200 mg/ml solution for subcutaneous injection
human normal immunoglobulin (SCIg)
For subcutaneous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 g/5 ml
2 g/10 ml
4 g/20 ml
10 g/50 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Hizentra 200 mg/ml solution for subcutaneous injection in pre-filled syringe
human normal immunoglobulin (SCIg)
For subcutaneous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 g/5 ml
2 g/10 ml
4 g/20 ml
10 g/50 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Hizentra 200 mg/ml solution for subcutaneous injection
Human normal immunoglobulin (SCIg = **S**ub**c**utaneous **I**mmuno**g**lobulin)

Read all of this leaflet carefully before you start using this medicine, because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or healthcare professional.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your healthcare professional. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hizentra is and what it is used for
2. What you need to know before you use Hizentra
3. How to use Hizentra
4. Possible side effects
5. How to store Hizentra
6. Contents of the pack and other information

1. What Hizentra is and what it is used for

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

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

What Hizentra is used for

Replacement therapy
Hizentra is used to raise abnormally low immunoglobulin levels in your blood to normal levels (replacement therapy). The medicine is used in adults and children (0-18 years) in the following situations:

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

2. *Treatment of patients with low or dysfunctional immunoglobulin levels in acquired conditions (secondary immunodeficiency) who experience severe or recurrent infections due to a weakened immune system resulting from other conditions or treatments.*

Immunomodulatory therapy in CIDP patients
Hizentra is also used in patients with chronic inflammatory demyelinating polyneuropathy (CIDP), a form of autoimmune disease. CIDP is characterised by chronic inflammation of the peripheral nerves that causes muscle weakness and/or numbness mainly in the legs and arms. It is believed that the body's defense attack underlines such inflammation, and the immunoglobulins present in Hizentra help to protect the nerves from being attacked (immunomodulatory therapy).

2. What you need to know before you use Hizentra

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

Warnings and precautions
➔ Talk to your doctor or healthcare professional before using Hizentra.

You may be allergic (hypersensitive) to immunoglobulins without knowing it. However, true allergic reactions are rare. They may occur even if you received human immunoglobulins previously and tolerated them well. It may happen particularly if you do not have enough of the immunoglobulin type A (IgA) in your blood (IgA deficiency).
➔ Tell your doctor or healthcare professional prior to treatment if you have an immunoglobulin type A (IgA) deficiency. Hizentra contains residual amounts of IgA which might cause an allergic reaction.
In these rare cases allergic reactions, such as a sudden fall in blood pressure or shock may occur (see also section 4 "Possible side effects").
➔ If you notice such signs during the infusion of Hizentra, stop the infusion and contact your doctor or go to the nearest hospital immediately.

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

➔ Contact your doctor if you experience the following signs and symptoms: severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting after receiving Hizentra. Your doctor will decide if further tests are necessary and whether Hizentra should be continued.

Your healthcare professional will avoid potential complications by ensuring:
- ► that you are not sensitive to human normal immunoglobulin.
  The medicine must be infused slowly at first. The recommended infusion rate given under section 3 "How to use Hizentra" must be closely followed.
- ► that you are carefully monitored for any symptoms throughout the infusion period, especially if:
  - you receive human normal immunoglobulin for the first time
  - you have switched from a different medicine

- there has been a long interval (more than eight weeks) since the previous infusion.

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

Other medicines and Hizentra

➔ Tell your doctor or healthcare professional if you are using, have recently used or might use any other medicines.

➔ You must not mix other medicines with Hizentra.

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

Pregnancy, breast-feeding and fertility

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

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

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

Driving and using machines

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

Hizentra contains proline

You must not take it if you suffer from hyperprolinaemia (see also section 2 “What you need to know before you use Hizentra”). Please tell your doctor prior to treatment.

Other important information about Hizentra

Blood tests

After receiving Hizentra, the results of certain blood tests (serological tests) may be impaired for a certain time.

➔ Tell your doctor about your treatment with Hizentra prior to any blood test.

Information on what Hizentra is made of

Hizentra is made from human blood plasma (this is the liquid part of the blood). When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, *and*
- the testing of each donation and pools of plasma for signs of virus/infections.

Manufacturers of these medicines also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

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

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

Hizentra contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial/syringe, that is to say essentially 'sodium-free'.

3. How to use Hizentra

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

Dosage
Your doctor will calculate the correct dose for you taking into account your weight and response to treatment.
The dose or dosing interval should not be changed without consulting your doctor.
If you think you should receive Hizentra more or less frequently, please speak to your doctor.
If you think you have missed a dose, speak to your doctor as soon as possible.

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

Immunomodulatory therapy
Your doctor will initiate therapy with Hizentra 1 week after your last intravenous immunoglobulin infusion by administrating under the skin (subcutaneously) with a weekly dose of 1.0 to 2.0 ml/kg of body weight. Your doctor will determine your weekly Hizentra dose. The weekly maintenance doses may be divided into smaller doses and administered as often as required during the week. For dosing every two weeks, your doctor will double the weekly Hizentra dose. Your healthcare professional may adjust the dose based on your response to the treatment.

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

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

Infusion site(s)
- Administer Hizentra under the skin only.
- You may infuse Hizentra into sites such as abdomen, thigh, upper arm, and lateral hip. If large doses are given (>50 ml), try to administer them at multiple sites.
- You may use an unlimited number of sites simultaneously. Injection sites should be at least 5 cm apart.

- In the case, you will use a device-assisted infusion technique (e.g. pump-assisted infusion), more than one infusion device can be used simultaneously.
- In the case, you will use the manual push infusion technique with a syringe, you may use only one infusion site per syringe. If you need to administer an additional Hizentra syringe, you must use a new sterile injection needle and change the infusion site.
- The volume of product infused into a particular site may vary.

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

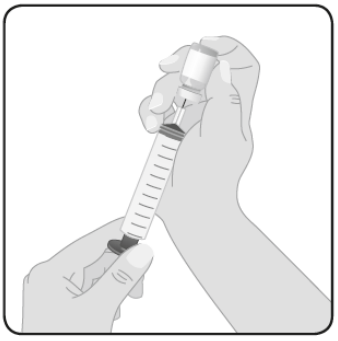
Device-assisted infusion:
The recommended initial infusion rate is up to 20 ml/hour/site. If well-tolerated, you may gradually increase the infusion rate to 35 ml/hour/site for the subsequent two infusions. Thereafter, the infusion rate can be increased further as per your tolerability.

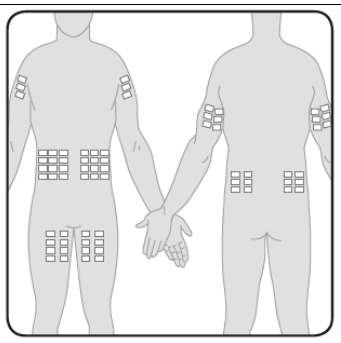
Manual push infusion:
The recommended initial infusion rate is up to 0.5 ml/min/site (30 ml/hour/site). If well-tolerated, you may increase the infusion rate up to 2.0 ml/min/site (120 ml/hour/site) for subsequent infusions. Thereafter, the infusion rate can be increased further as per your tolerability.

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.
  </td></tr>
<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>
</table>

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

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

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

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

4. Possible side effects

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

► In isolated cases, you may be allergic (hypersensitive) to immunoglobulins and allergic reactions such as a sudden fall in blood pressure or shock may occur (e.g. you may feel light-

headed, dizzy, faint on standing, cold in the hands and feet, sense an abnormal heart beat or chest pain, or have blurred vision).

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

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

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

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

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

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

The following side effects are **common** (affects 1 to 10 patients in 100):
- Dizziness
- Migraine
- Increased blood pressure (hypertension)
- Diarrhoea
- Abdominal pain
- Feeling sick (nausea)
- Vomiting
- Itching (pruritus)
- Hives (urticaria)
- Pain related to the musculature and bones (musculoskeletal pain)
- Joint pain (arthralgia)
- Fever
- Tiredness (fatigue), including generally feeling unwell (malaise)
- Chest pain
- Flu-like symptoms
- Pain

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

In isolated cases, infusion site ulcer or burning sensation may occur.

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

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

Please also refer to section 2 “What you need to know before you use Hizentra” for additional details on circumstances which increase the risk of side effect.

Reporting of side effects
If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hizentra

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton and the vial label after EXP.
- You must use/infuse this medicine as soon as possible after opening the vial. Do not use Hizentra if the vial is open or defective.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your healthcare professional how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Hizentra contains
- The **active substance** is human normal immunoglobulin. One ml contains 200 mg of human normal immunoglobulin, of which at least 98% is immunoglobulin type G (IgG).
  The approximate percentage of IgG subclasses is as follows:
  IgG1 .....69%
  IgG2 .....26%
  IgG3 .....3%
  IgG4 .....2%
  This medicine contains trace amounts of IgA (not more than 50 micrograms /ml).

- The **other ingredients** (excipients) are L-proline, polysorbate 80 and water for injections.

What Hizentra looks like and contents of the pack
Hizentra is a solution for subcutaneous injection (200 mg/ml). The colour can vary from pale-yellow to light-brown.
Hizentra is available in vials of 5, 10, 20 or 50 ml.
Hizentra is also available in pre-filled syringes of 5, 10, 20 and 50 ml.

Pack sizes
Packs of 1, 10, or 20 vials

Hizentra is also available in packs of 1 (for 5, 10, 20, 50 ml), 10 (for 5, 10, 20, 50 ml), or 20 (for 10, 20 ml) pre-filled syringes.
Please note that alcohol swabs, needles and other supplies or equipment are not contained in the pack.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the user

Hizentra 200 mg/ml solution for subcutaneous injection in pre-filled syringe
Human normal immunoglobulin (SCIg = **S**ub**c**utaneous **I**mmuno**g**lobulin)

Read all of this leaflet carefully before you start using this medicine, because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or healthcare professional.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your healthcare professional. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hizentra is and what it is used for
2. What you need to know before you use Hizentra
3. How to use Hizentra
4. Possible side effects
5. How to store Hizentra
6. Contents of the pack and other information

1. What Hizentra is and what it is used for

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

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

What Hizentra is used for

Replacement therapy
Hizentra is used to raise abnormally low immunoglobulin levels in your blood to normal levels (replacement therapy). The medicine is used in adults and children (0-18 years) in the following situations:

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

2. *Treatment of patients with low or dysfunctional immunoglobulin levels in acquired conditions (secondary immunodeficiency) who experience severe or recurrent infections due to a weakened immune system resulting from other conditions or treatments.*

Immunomodulatory therapy in CIDP patients
Hizentra is also used in patients with chronic inflammatory demyelinating polyneuropathy (CIDP), a form of autoimmune disease. CIDP is characterised by chronic inflammation of the peripheral nerves that causes muscle weakness and/or numbness mainly in the legs and arms. It is believed that the body's defense attack underlines such inflammation, and the immunoglobulins present in Hizentra help to protect the nerves from being attacked (immunomodulatory therapy).

2. What you need to know before you use Hizentra

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

Warnings and precautions
➔ Talk to your doctor or healthcare professional before using Hizentra.

You may be allergic (hypersensitive) to immunoglobulins without knowing it. However, true allergic reactions are rare. They may occur even if you received human immunoglobulins previously and tolerated them well. It may happen particularly if you do not have enough of the immunoglobulin type A (IgA) in your blood (IgA deficiency).
➔ Tell your doctor or healthcare professional prior to treatment if you have an immunoglobulin type A (IgA) deficiency. Hizentra contains residual amounts of IgA which might cause an allergic reaction.
In these rare cases allergic reactions, such as a sudden fall in blood pressure or shock may occur (see also section 4 "Possible side effects").
➔ If you notice such signs during the infusion of Hizentra, stop the infusion and contact your doctor or go to the nearest hospital immediately.

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

➔ Contact your doctor if you experience the following signs and symptoms: severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting after receiving Hizentra. Your doctor will decide if further tests are necessary and whether Hizentra should be continued.

Your healthcare professional will avoid potential complications by ensuring:
- ► that you are not sensitive to human normal immunoglobulin.
  The medicine must be infused slowly at first. The recommended infusion rate given under section 3 "How to use Hizentra" must be closely followed.
- ► that you are carefully monitored for any symptoms throughout the infusion period, especially if:
  - you receive human normal immunoglobulin for the first time
  - you have switched from a different medicine

- there has been a long interval (more than eight weeks) since the previous infusion.

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

Other medicines and Hizentra

➔ Tell your doctor or healthcare professional if you are using, have recently used or might use any other medicines.

➔ You must not mix other medicines with Hizentra.

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

Pregnancy, breast-feeding and fertility

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

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

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

Driving and using machines

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

Hizentra contains proline

You must not take it if you suffer from hyperprolinaemia (see also section 2 “What you need to know before you use Hizentra”). Please tell your doctor prior to treatment.

Other important information about Hizentra

Blood tests

After receiving Hizentra, the results of certain blood tests (serological tests) may be impaired for a certain time.

➔ Tell your doctor about your treatment with Hizentra prior to any blood test.

Information on what Hizentra is made of

Hizentra is made from human blood plasma (this is the liquid part of the blood). When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, *and*
- the testing of each donation and pools of plasma for signs of virus/infections.

Manufacturers of these medicines also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

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

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

Hizentra contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial/syringe, that is to say essentially 'sodium-free'.

3. How to use Hizentra

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

Dosage
Your doctor will calculate the correct dose for you taking into account your weight and response to treatment.
The dose or dosing interval should not be changed without consulting your doctor.
If you think you should receive Hizentra more or less frequently, please speak to your doctor.
If you think you have missed a dose, speak to your doctor as soon as possible.

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

Immunomodulatory therapy
Your doctor will initiate therapy with Hizentra 1 week after your last intravenous immunoglobulin infusion by administrating under the skin (subcutaneously) with a weekly dose of 1.0 to 2.0 ml/kg of body weight. Your doctor will determine your weekly Hizentra dose. The weekly maintenance doses may be divided into smaller doses and administered as often as required during the week. For dosing every two weeks, your doctor will double the weekly Hizentra dose. Your healthcare professional may adjust the dose based on your response to the treatment.

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

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

Infusion site(s)
- Administer Hizentra under the skin only.
- You may infuse Hizentra into sites such as abdomen, thigh, upper arm, and lateral hip. If large doses are given (>50 ml), try to administer them at multiple sites.
- You may use an unlimited number of sites simultaneously. Injection sites should be at least 5 cm apart.

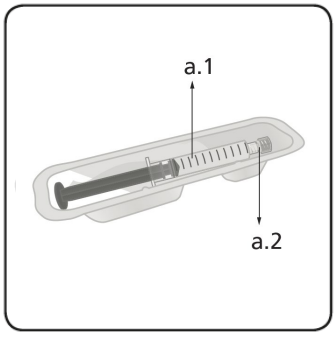
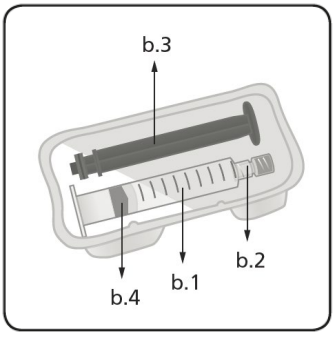
- In the case, you will use a device-assisted infusion technique (e.g. pump-assisted infusion), more than one infusion device can be used simultaneously.
- In the case, you will use the manual push infusion technique with a syringe, you may use only one infusion site per syringe. If you need to administer an additional Hizentra syringe, you must use a new sterile injection needle and change the infusion site.
- The volume of product infused into a particular site may vary.

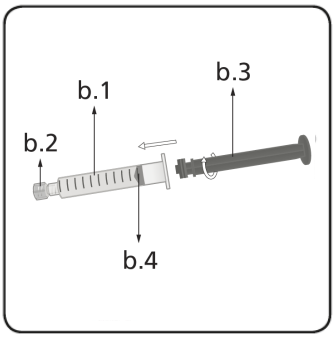
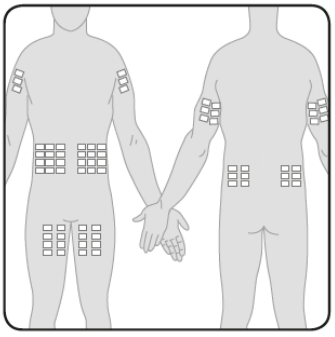
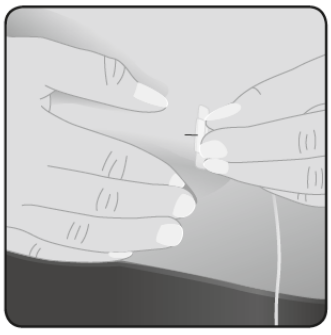
Infusion rate(s)
Your doctor will determine the appropriate infusion technique and the infusion rate for you taking into account your individual dose, dosing frequency and product tolerability.

Device-assisted infusion:
The recommended initial infusion rate is up to 20 ml/hour/site. If well-tolerated, you may gradually increase the infusion rate to 35 ml/hour/site for the subsequent two infusions. Thereafter, the infusion rate can be increased further as per your tolerability.

Manual push infusion:
The recommended initial infusion rate is up to 0.5 ml/min/site (30 ml/hour/site). If well-tolerated, you may increase the infusion rate up to 2.0 ml/min/site (120 ml/hour/site) for subsequent infusions. Thereafter, the infusion rate can be increased further as per your tolerability.

Instructions for use

Follow the steps below and use aseptic technique to administer Hizentra.	
1	**Clean surface** Thoroughly clean a table or other flat surface using an antiseptic wipe.
2	**Assemble supplies** Place Hizentra and other supplies and equipment needed for the infusion on a clean, flat surface.
3	**Thoroughly wash and dry hands**
4	**Check blistered pre-filled syringes** Visually inspect Hizentra for particles in the solution or discoloration as well as expiry date before administering Hizentra**.** Do not use solutions that are cloudy or contain particles. Do not use solutions that have been frozen. Administer solution which is at room or body temperature. Once a blistered pre-filled syringe has been opened, use the solution immediately. Please dispose of the oxygen absorber pack (which can be found underneath the syringe). 
5	**Preparation of Hizentra for infusion** The 5 ml, 10 ml, 20 and 50 ml pre-filled syringes are supplied ready to use. The 5 ml and 10 ml pre-filled syringes (a.1) are fully assembled.  For the 20 ml and 50 ml pre-filled syringe (b.1), screw the plunger rod (b.3) onto the pre-filled syringe stopper with inside thread (b.4) prior to use. 

	All pre-filled syringes have a standard luer lock (a.2 and b.2), which is a screw connection at the syringe tip that creates a leak-free seal. If you are using a syringe pump, Hizentra pre-filled syringes can be placed directly in the syringe pump if the syringe size matches the pump requirements. If the pre-filled syringe can be placed directly in the pump, then go to Step 6. If the Hizentra pre-filled syringe size does not match the pump requirements, then the contents of the pre-filled syringe can be transferred to another syringe of a size specific for the pump. 
6	**Prepare the tubing** Attach the administration tubing or needle set to the syringe. Prime the tubing to eliminate all remaining air.
7	**Prepare infusion site(s)** **Select the infusion site(s) –** The number and location of infusion sites depends on the volume of the total dose. Each infusion site should be at least 5 cm apart. You may use an unlimited number of sites simultaneously.  **Clean the infusion site(s)** using an antiseptic skin preparation, Allow each site to dry before proceeding.
8	**Insert the needle** Grasp the skin between 2 fingers and insert the needle into the subcutaneous tissue. **Secure the needle to the skin** – If necessary, use gauze and tape or transparent dressing to hold the needle in place. 
9	**Infuse Hizentra** Start infusion. If using an infusion pump, follow the manufacturer's instructions.
10	**Record the infusion** Record the following data in your treatment diary: • the date of administration, • the batch number of the medicine, and • the infused volume, flow rate, the number and location of infusion sites.
11	**Clean up** Dispose of any unused product and all used administration supplies after administration together with the oxygen absorber pack in accordance with local requirements.

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

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

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

4. Possible side effects

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

- ► In isolated cases, you may be allergic (hypersensitive) to immunoglobulins and allergic reactions such as a sudden fall in blood pressure or shock may occur (e.g. you may feel light-headed, dizzy, faint on standing, cold in the hands and feet, sense an abnormal heart beat or chest pain, or have blurred vision).
- ► In isolated cases, you may experience pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body, sudden confusion, or trouble speaking or understanding could be signs of a blood clot.
- ► In isolated cases, you may get a bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light, which could be signs of AMS (aseptic meningitis sydrome), which is a temporary reversible non-infectious inflammation of the membranes surrounding the brain and the spinal cord.

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

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

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

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

The following side effects are **common** (affects 1 to 10 patients in 100):
- Dizziness
- Migraine
- Increased blood pressure (hypertension)
- Diarrhoea
- Abdominal pain
- Feeling sick (nausea)
- Vomiting
- Itching (pruritus)
- Hives (urticaria)
- Pain related to the musculature and bones (musculoskeletal pain)
- Joint pain (arthralgia)
- Fever
- Tiredness (fatigue), including generally feeling unwell (malaise)

- Chest pain
- Flu-like symptoms
- Pain

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

In isolated cases, infusion site ulcer or burning sensation may occur.

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

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

Please also refer to section 2 “What you need to know before you use Hizentra” for additional details on circumstances which increase the risk of side effect.

Reporting of side effects
If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hizentra

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton and the pre-filled syringe label after EXP.
- You must use/infuse this medicine as soon as possible after opening the blistered pre-filled syringe. Do not use Hizentra if the blistered pre-filled syringe is open or defective.
- Do not store above 25 °C.
- Do not freeze.
- Keep the blistered pre-filled syringe in the outer carton in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask your healthcare professional how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Hizentra contains
- The **active substance** is human normal immunoglobulin. One ml contains 200 mg of human normal immunoglobulin, of which at least 98% is immunoglobulin type G (IgG).
  The approximate percentage of IgG subclasses is as follows:
  IgG1 .....69%
  IgG2 .....26%
  IgG3 .....3%

IgG4 .....2%
This medicine contains trace amounts of IgA (not more than 50 micrograms /ml).

- The **other ingredients** (excipients) are L-proline, polysorbate 80 and water for injections.

What Hizentra looks like and contents of the pack
Hizentra is a solution for subcutaneous injection (200 mg/ml). The colour can vary from pale-yellow to light-brown.
Hizentra is available in pre-filled syringes of 5, 10, 20 or 50 ml. Each pre-filled syringe is packed in a blister that contains an oxygen absorber pack to protect from discoloration. Please dispose of the oxygen absorber pack.

Hizentra is also available in vials of 5, 10, 20 and 50 ml.

Pack sizes
Packs of 1 (for 5, 10, 20, 50 ml), 10 (for 5, 10, 20, 50 ml) or 20 (for 10, 20 ml) pre-filled syringes.
Hizentra is also available in packs of 1, 10, or 20 vials.

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

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.
