SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hizentra 200 mg/ml solution for subcutaneous injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (SCIg)

One ml contains: Human plasma protein……..200 mg
(purity of at least 98% IgG)

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 ..... 62-74%
IgG2 ..... 22-34%
IgG3 ..... 2-5%
IgG4 ..... 1-3%

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),
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated,

- Hypogammaglobulinaemia and recurrent infections in multiple myeloma (MM) patients,
- Hypogammaglobulinaemia in patients pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT).

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a healthcare professional experienced in the treatment of immunodeficiency.

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 pharmacokinetic and clinical response and serum IgG trough levels. The following dose regimens are given as a guideline.

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l and aim to be within the reference interval of serum IgG for 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 anatomical 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.

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 33 paediatric subjects (21 children [3 to 11 years] and 12 adolescents [12 to 16 years]) with primary immunodeficiency disease (PID). No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

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 of adults.

Method of administration

For subcutaneous use only.

Subcutaneous infusion for home treatment should 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 the infusion device, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

Hizentra may be injected into sites such as abdomen, thigh, upper arm, and lateral hip.
The recommended initial infusion rate depends on individual needs of the patient and should not exceed 15 ml/hour/site. If well-tolerated (see also section 4.4), the infusion rate can then gradually be increased to 25 ml/hour/site for the following two infusions.

More than one infusion device can be used simultaneously. The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 ml. In adults, doses over 30 ml may be divided according to patient preference. There is no limit to the number of infusion sites. Infusion sites should be at least 5 cm apart.

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 naive 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.

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.

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.

Interference with serological testing

After injection 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
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.

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

Hizentra has no or negligible influence on the ability to drive and 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 from one phase I study with healthy subjects (n = 28) and two phase III studies in patients with primary immunodeficiency (n = 100) with Hizentra.
The ARs reported in these three clinical studies are summarised and categorised according to the MedDRA System Organ Class and frequency below. Frequency 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), and rare (≥1/10,000 to <1/1,000).

Frequency of Adverse Reactions (ARs) in clinical studies with Hizentra

System Organ Class (SOC, MedDRA)	**Frequency of ARs** (MedDRA Preferred Term, PT)			
	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)
Infections and Infestations				Nasopharyngitis
Immune system disorders				Hypersensitivity
Nervous system disorders		Headache		Dizziness, migraine, psychomotor hyperactivity, somnolence
Cardiac disorders				Tachycardia
Vascular disorders				Haematoma, hot flush
Respiratory, thoracic and mediastinal disorders				Cough

System Organ Class (SOC, MedDRA)	**Frequency of ARs** (MedDRA Preferred Term, PT)			
	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)
Gastrointestinal disorders			Vomiting	Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, diarrhoea, nausea
Skin and subcutaneous tissue disorders			Pruritus	Dermatitis contact, erythema, rash, urticaria
Musculoskeletal and connective tissue disorders				Arthralgia, back pain, muscle spasms, muscular weakness, musculoskeletal pain, myalgia, neck pain, pain in extremity
Renal and urinary disorders				Haematuria
General disorders and administration site conditions	Injection/ infusion site reactions		Fatigue, pain	Chest pain, chills, feeling cold, hypothermia, influenza like illness, malaise, pyrexia
Investigations				Aldolase increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood pressure increased, body temperature increased, weight decreased
Injury, poisoning and procedural complications				Contusion

In addition to the ADRs listed above, the following adverse reactions have been identified during post-approval use of Hizentra:
Immune system disorders: anaphylactic reactions
Nervous system disorders: aseptic meningitis syndrome (AMS), lethargy, tremor, burning sensation
Vascular disorders: thromboembolism
General disorders and administration site conditions: infusion site ulcer

Reliable estimates of the frequency of these reactions or establishment of a causal relationship to product exposure are not possible because the reporting is voluntary and from a population of uncertain size.

<u>Paediatric population</u>

The same adverse reactions may occur in the paediatric population. Please refer to section 4.4 for details on risk factors and monitoring recommendations.

Elderly population
The same adverse reactions may occur in the elderly population.

Limited information available from clinical trials showed no difference in the safety profile of patients ≥ 65 years of age than of younger patients.

Post-marketing 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:

UK: Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard

Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; website: www.hpra.ie; Email: medsafety@hpra.ie

Malta: ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

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. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

In the European 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. 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 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 body weight. Sustained IgG trough levels with a mean concentration of 12.53 g/l were thereby achieved throughout the treatment period. Subjects received in total 2,264 weekly Hizentra infusions.
No serious bacterial infections were reported during the efficacy period in subjects receiving Hizentra during clinical studies.

Paediatric population
No differences were seen in the pharmacodynamic properties between adult and paediatric study patients.

Elderly population
No differences were seen in the pharmacodynamic properties between adult and elderly study patients.

5.2 Pharmacokinetic properties

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

In a clinical 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 body weight.

Simulations by empirical Population Pharmacokinetic models suggest that comparable IgG exposure levels ($AUC_{0\text{-}14days}$, $C_{min\ 14\ days}$) may be obtained if Hizentra is administered subcutaneously every two weeks using double the weekly dose during maintenance therapy.

These simulations further suggest 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.

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

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

Elderly population
No differences were seen in the pharmacokinetic parameters between adult and elderly study patients.

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 store above 25 °C.
Do not freeze.
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

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

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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/687/001: 1g / 5ml, 1 vial
EU/1/11/687/002: 1g / 5ml, 10 vials
EU/1/11/687/003: 1g / 5ml, 20 vials
EU/1/11/687/004: 2g / 10ml, 1 vial
EU/1/11/687/005: 2g / 10ml, 10 vials
EU/1/11/687/006: 2g / 10ml, 20 vials
EU/1/11/687/010: 4g / 20ml, 1 vial
EU/1/11/687/011: 4g / 20ml, 10 vials
EU/1/11/687/012: 4g / 20ml, 20 vials
EU/1/11/687/013: 10g / 50ml, 1 vial
EU/1/11/687/014: 10g / 50ml, 10 vials

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

14 April 2011 / 18 February 2016

10. DATE OF REVISION OF THE TEXT

20 February 2017

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