ANNEX I

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)

One vial of 5 ml solution contains: 1 g of human plasma protein
One vial of 10 ml solution contains: 2 g of human plasma protein
One vial of 15 ml solution contains: 3 g of human plasma protein
One vial of 20 ml solution contains: 4 g of human plasma protein

Approximate distribution of the IgG subclasses:
IgG1.....62-74%
IgG2.....22-34%
IgG3.....2-5%
IgG4.....1-3%

The maximum IgA content is 0.050 mg/ml.

Produced from the plasma of human donors.

Hizentra is essentially sodium free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults and children in primary immunodeficiency syndromes such as:
- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- IgG subclass deficiencies with recurrent infections

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

4.2 Posology and method of administration

Treatment should be commenced and initially monitored under the supervision of a healthcare professional experienced in the treatment of immunodeficiency.

Posology
Adults and children

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 using the subcutaneous route should achieve a sustained level of IgG. A loading dose of at least 0.2 to 0.5 g/kg (1.0 to 2.5 ml/kg) body weight may be required. This may need to be divided over several days. After steady state IgG levels have been attained, maintenance doses are 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.

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.

As the posology is given by body weight and adjusted to the clinical outcome of the above mentioned conditions, the posology in the paediatric population is not considered to be different to that of adults.

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.

Method of administration
The medicinal product must be administered via the subcutaneous route only. Hizentra may be injected into sites such as abdomen, thigh, upper arm, and lateral hip. If large doses are given (> 25 ml), it is advisable to administer them at multiple sites.

The recommended initial infusion rate depends on individual needs of the patient and should not exceed 15 ml/hour/site (see also section 4.4). If well-tolerated, the infusion rate can then gradually be increased to 25 ml/hour/site.
Infusion pumps appropriate for subcutaneous administration of immunoglobulins can be used.
Up to 4 injection sites can be used simultaneously, provided that the maximum infusion rate for all sites combined does not exceed 50 ml/hour. Injection sites should be at least 5 cm apart.

Subcutaneous infusion for home treatment should be commenced and initially monitored by a healthcare professional experienced in the guidance of patients for home treatment. The patient or a caregiver will be instructed in infusion techniques, the keeping of a treatment diary and measures to be taken in case of severe adverse reactions.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Patients with hyperprolinaemia.
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.

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.

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 signs. 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.

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).

4.5 Interaction 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.

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 and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus or the neonate are to be expected.
Continued treatment of the pregnant woman ensures a passive immunity for the neonate.

Breast-feeding
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 summary 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	**Frequency of ARs** (MedDRA Preferred Term, PT)

Class (SOC, MedDRA)	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
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

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.

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.

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.

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

2 years.
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.

6.5 Nature and contents of container

5, 10, 15 or 20 ml of solution in a vial (type I 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
3 g / 15 ml
4 g / 20 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 at room or body temperature before use.

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER 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

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.2 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

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 plasma protein ..... 200 mg
IgG purity ..... ≥ 98%
IgA..... ≤ 0.050 mg

1 g/5 ml
2 g/10 ml
3 g/15 ml
4 g/20 ml

3. LIST OF EXCIPIENTS

Excipients: L-proline, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 x 5 ml
1 x 10 ml
1 x 15 ml
1 x 20 ml
10 x 5 ml
10 x 10 ml
10 x 15 ml
10 x 20 ml
20 x 5 ml
20 x 10 ml
20 x 15 ml
20 x 20 ml

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Hizentra

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
3 g/15 ml
4 g/20 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 taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or healthcare professional.

In this leaflet:

1. What Hizentra is and what it is used for
2. Before you use Hizentra
3. How to use Hizentra
4. Possible side effects
5. How to store Hizentra
6. Further 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. The medicine works in exactly the same way as the immunoglobulins naturally present in your blood.

What Hizentra is used for

Hizentra is used to raise abnormally low immunoglobulin levels in your blood to normal levels (replacement therapy). The medicine is used in two different situations:

1. Treatment of adults and children 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 adults and children with certain kinds of blood cancer (such as myeloma or chronic lymphocytic leukaemia) which lead to severely low immunoglobulin levels in the blood and cause recurrent infections.

2. BEFORE YOU USE HIZENTRA

Do **NOT** inject Hizentra:

► if you are allergic (hypersensitive) 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.

Take special care with 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). In these rare cases 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).
➔ If you notice such signs during the infusion of Hizentra, tell your doctor immediately. He or she will decide whether to slow down the infusion rate or whether to stop the infusion completely.

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.

<u>Blood tests</u>
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.

<u>Information on what Hizentra is made of</u>
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 recommended that every time you take Hizentra the following data are recorded in your treatment diary:
  - the date of administration,
  - the batch number of the medicine, and
  - the injected volume, flow rate, the number and location of injection sites.

Taking other medicines

➔ Tell your doctor or healthcare professional prior to treatment
- if you are currently taking any other medicines or
- if you have recently taken any other medicines.

This also includes non-prescription medicines.

You must not mix other medicines with Hizentra.

Vaccinations
Hizentra may impair the effect of some live virus vaccines such as measles, rubella, mumps and chicken pox. Therefore, after receiving these medicines 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.

Therefore your vaccinating doctor should check the efficacy of the measles vaccination.
➔ Tell your vaccinating doctor prior to a vaccination about your treatment with Hizentra.

Pregnancy and breast-feeding

➔ 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

No effects of Hizentra on the ability to drive and use machines are expected.

Important information about some of the ingredients of Hizentra

Hizentra contains proline and you must not take it if you suffer from hyperprolinaemia (see also section 2 “Before you use Hizentra”). Please tell your doctor prior to treatment.
Hizentra is essentially sodium free.
➔ 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.

3. HOW TO USE HIZENTRA

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

Your doctor will calculate the correct dose for you taking into account your weight and response to treatment.

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,

usually weekly, 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.

Method of administration

In case of home treatment, this will be initiated by a healthcare professional experienced in the treatment of immunodeficiency and in the guidance of patients for home treatment.

- You will be instructed in:
  - aseptic infusion techniques
  - the keeping of a treatment diary, and
  - measures to be taken in case of severe side effects.
- Hizentra is a ready-to-use solution (see section 5 “How to store Hizentra” and section 6 “What Hizentra looks like and contents of the pack”).
- 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.
- Administer Hizentra under the skin only.
- You may inject Hizentra into sites such as abdomen, thigh, upper arm, and lateral hip. If large doses are given (> 25 ml), try to administer them at multiple sites.
- The recommended initial infusion rate is up to 15 ml/hour/site. If well-tolerated, the infusion rate can then gradually be increased to 25 ml/hour/site.
- You may use up to 4 injections sites simultaneously, provided that the maximum infusion rate for all sites combined does not exceed 50 ml/hour. Injection sites should be at least 5 cm apart.
- Once an injection vial has been opened, use the solution immediately.

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 use less Hizentra than you should

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Hizentra can have side effects, although not everybody gets them.

► 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).
➔ If you notice such signs during the infusion of Hizentra, tell your doctor immediately. Please see also section 2 of this leaflet about the risk of allergic reactions.

► Possible side effects may be reduced or even avoided, by infusing Hizentra slowly.

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

The following side effects are **common** (affects 1 to 10 infusions in 100):
- Headache

The following side effects are **uncommon** (affects 1 to 10 infusions in 1,000):
- Vomiting
- Itching (pruritus)
- Tiredness (fatigue)
- Pain

The following side effects are **rare** (affects 1 to 10 infusions in 10,000):
- Common cold symptoms
- Hypersensitivity
- Dizziness
- Migraine
- Restlessness
- Sleepiness (somnolence)
- Fast heartbeat
- Bruising (haematoma and contusion)
- Hot flushes
- Cough
- Abdominal discomfort, distension, upper or lower abdominal pain
- Diarrhoea
- Feeling sick (nausea)
- Skin reactions such as irritation, redness, rash, blister
- Joint pain (arthralgia)
- Muscle weakness, spasms, aching muscles (myalgia)
- Pain in neck, back, chest, arms and/or legs
- Pain related to the musculature and bones (musculoskeletal pain)
- Blood in the urine (haematuria)
- Chills, feeling cold, low body temperature (hypothermia)
- Flu-like symptoms
- Generally feeling unwell (malaise)
- Fever
- Results of blood tests suggesting impaired liver and kidney function
- High blood pressure
- Weight loss

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

➔ Tell your doctor or healthcare professional
- if any of the side effects get serious or
- if you notice any side effects not listed in this leaflet.

5. HOW TO STORE HIZENTRA

- Keep out of the reach and sight of children.
- Do not use after the expiry date which is stated on the outer carton and the vial label after EXP.
- Because the solution contains no preservative, Hizentra should be used/infused as soon as possible after opening the vial.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Medicines should not be disposed of via wastewater or household waste. Ask your healthcare professional how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Hizentra contains

- The **active substance** is human normal immunoglobulin. One ml contains 200 mg of human plasma protein, of which at least 98% is immunoglobulin type G (IgG).
  The approximate percentage of IgG subclasses is as follows:
  IgG1 .....62-74%
  IgG2 .....22-34%
  IgG3 .....2-5%
  IgG4 .....1-3%
  This medicine contains trace amounts of IgA (not more than 0.050 mg/ml).
  Hizentra is essentially sodium free.

- The **other ingredients** 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, 15 or 20 ml.

Pack sizes
Packs of 1, 10 or 20 vials
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

CSL Behring GmbH
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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