

Product Information

Hizentra[®]

Australia

NAME OF THE MEDICINE

Normal immunoglobulin (Human) 20% (20 g/100 mL), subcutaneous injection.

DESCRIPTION

Hizentra[®] is a sterile, clear and colourless or pale yellow or light brown solution of human normal immunoglobulin for subcutaneous injection.

Hizentra[®] is a 20% solution containing 20 g/100 mL of total human plasma protein with a purity of at least 98% immunoglobulin G (IgG). More than 90% of the IgG consists of monomers and dimers, aggregates ($\leq 2\%$ —typically below 0.1%). The distribution of the IgG subclasses is similar to that found in normal human plasma (approximate mean values: 68% IgG₁, 27% IgG₂, 3% IgG₃, 2% IgG₄).

Hizentra[®] has a nominal osmolality of 380 mOsmol/kg and is approximately isotonic. The pH value of the ready-to-use solution is 4.8. The product contains 250 mmol/L of proline as a stabiliser which is a physiological non-essential amino acid. The product also contains trace amounts of Polysorbate 80 and sodium. Hizentra[®] contains no carbohydrate stabiliser (e.g. sucrose, maltose) and no preservative.

The maximum IgA content is 0.05 mg/mL (normally below 0.005 mg/mL).

The manufacturing process for Hizentra[®] includes three steps to reduce the possibility of virus transmission. Two of these are dedicated virus clearance steps: pH 4 incubation to inactivate enveloped viruses and nanofiltration to remove, by size exclusion, both enveloped and non-enveloped viruses as small as approximately 20 nanometres. In addition, a depth filtration step contributes to the virus reduction capacity.

PHARMACOLOGY

Pharmacodynamics

Hizentra[®] contains the IgG antibodies present in the normal population. It is prepared from pooled plasma collected from not fewer than 1000 donors. It has a distribution of IgG subclasses closely proportional to that in native human plasma.

Hizentra[®] contains functionally intact IgG with a broad spectrum of antibodies against infectious agents. The Fc and Fab functions of the IgG molecule are retained.

Adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range.

Pharmacokinetics

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

In a clinical trial with Hizentra[®] (n = 46), subjects achieved sustained trough levels (median 8.1 g/L) over a period of 28 (\pm 1) weeks when receiving median weekly doses of 0.06 to 0.24 g/kg body weight.

The pharmacokinetics were evaluated in a subset of 23 subjects with Primary Immunodeficiency (PID). A peak IgG concentration of 8.26 g/L and a trough IgG concentration ranging from 7.99 to 8.25 g/L were observed during the 28 (\pm 1) week pharmacokinetics evaluation period (refer to **Table 1**).

Table 1: Steady-State Pharmacokinetic Parameters of Hizentra[®] in 23 PID patients from the pivotal EU study

Parameter	Study ZLB06_001CR
Mean (SD) C _{max} (peak, g/L)	8.26 (1.255)
Mean (range) C _{min} (trough, g/L)	8.10 (7.99–8.25)
Median (range) T _{max} (days)	2.06 (0.94–6.92)
Mean (SD) AUC τ (day x g/L)	53.61 (9.984)

C_{max}: maximum serum IgG concentration

C_{min}: trough (minimum) serum IgG concentration

T_{max}: timepoint of maximum concentration

AUC τ : area under the c concentration–time curve during regular dosing interval

SD: standard deviation

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.

CLINICAL TRIALS

Treatment of Primary Immunodeficiency Diseases (PID)

Hizentra[®] has been evaluated in three pivotal Phase III studies in primary immunodeficiency subjects.

In the prospective, open-label, multicenter, single-arm European study, a total of 51 subjects aged between 3 and 60 years were enrolled from previous treatment with IVIG (60.9%) or SCIG (39.1%) and switched to Hizentra[®]. The objectives of the study were to investigate the efficacy, tolerability, safety, pharmacokinetics, and HRQL (Health Related Quality of Life) of Hizentra[®] in subjects with PID.

Hizentra[®] was administered subcutaneously for up to 41 weeks, at a dose equivalent to the previous Ig dose. The mean dose administered each week was 0.12 g/kg body weight, over a median infusion duration up to 1.25 hours during the wash-in/wash-out period; and up to 1.27 hours during the efficacy period (weeks 13 to 40). Subjects received in total 1831 weekly Hizentra[®] infusions.

The primary endpoint was to demonstrate in the ITT population (n = 46) sustained total serum IgG trough values, comparable to those observed with the previous IgG treatment. The mean of individual median IgG trough values increased by 8.1% with Hizentra[®] treatment (from 7.49 g/L with the previous IgG therapy to 8.10 g/L during Infusions 12 to 17), thus meeting the primary endpoint.

No Serious Bacterial Infections (SBIs) were reported during the efficacy period. The annual rate of total infections/subject/year was 5.18 (95% confidence limits: 4.305; 6.171). Twenty subjects in the ITT population (43.5%) missed work/school/kindergarten/day-care or were unable to perform normal activities due to infections for 198 days, equating to an annual rate of 8.00 days/subject/year. Four subjects (8.7%) were hospitalized due to infections during the efficacy period for a total of 86 days, with an annual rate of 3.48 days/subject/year.

Thirty-two subjects (69.6%) were treated with antibiotics on 1743 days, with an annual rate of 72.75 days/subject/year.

Some aspects of HRQL and treatment satisfaction improved with Hizentra[®] treatment compared to previous IVIG treatment, with statistically significant improvements from baseline observed for the Treatment Satisfaction Questionnaire for Medication (TSQM) domain convenience and for the total Life Quality Index (LQI) score. No differences were observed for Hizentra[®] compared to previous SCIG treatment.

In the US a prospective, open-label, multicenter, single-arm, clinical study evaluated the efficacy, tolerability, and safety of Hizentra[®] in 49 adult and paediatric PID subjects, 2 to 75 years of age. Subjects previously receiving monthly treatment with IVIG were switched to weekly subcutaneous administration of Hizentra[®] for 15 months (a 3-month wash-in/wash-out period followed by a 12-month efficacy period). The efficacy analyses included 38 subjects in the modified intention-to-treat (MITT) population. The primary endpoint was annual rate of SBIs per subject.

A dose adjustment co-efficient was applied when switching from IVIG to Hizentra[®] to ensure comparable systemic IgG exposure. Weekly doses of Hizentra[®] ranged from 0.07 to 0.38 g/kg which was 149% (range: 114% to 180%) of the previous IVIG dose. Subjects received a total of 2264 infusions. The number of injection sites per infusion ranged from 1 to 12, with ≤4 used in 73% of infusions. The maximum infusion rate during the study was 50 mL/hour for all simultaneous injection sites combined. The median duration of a weekly infusion ranged from 1.6 to 2.0 hours.

The annual SBI rate per subject was zero (upper 99% confidence limit: 0.132), thus achieving the primary efficacy endpoint.

Sustained IgG trough levels with a mean concentration of 12.53 g/L were achieved throughout the treatment period. The annual rate of any infections was 2.76 infections/subject/year (95% CI: 2.235; 3.370), in 31 subjects (81.6%). 12 subjects (31.6%) missed work/school/kindergarten/day care or were unable to perform normal activities on 71 days, with an annual rate of 2.06 days/subject/year. One subject was hospitalized seven days due to infections, equating to an annual rate of 0.20 days/subject year. Twenty-seven subjects (71.1%) were treated with antibiotics on 1688 days, with an annual rate of 48.5 days/subject/year.

The Japanese multicentre, single-arm, prospective, open-label, Phase III study evaluated the efficacy, safety, tolerability, health-related quality of life (HRQL), pharmacoeconomics (PE), and PK of Hizentra[®] in subjects with PID.

25 adult and paediatric subjects who were receiving regular IVIG treatment received 3 prospective IVIG infusions, followed by weekly subcutaneous Hizentra[®] infusions for up to 24 weeks, at doses equal to their previous IVIG weekly equivalent dose. Primary efficacy analysis was based on 21 patients in the per protocol group.

Patients received in total 584 weekly infusions. The mean dose administered in the efficacy period was 87.81 mg/kg body weight. Sustained IgG trough levels with mean IgG concentrations of 7.21–7.53 g/L were achieved throughout the efficacy period. There was an increase in the mean of individual median IgG trough values of 9% following switch to Hizentra[®], from 6.53 g/L in the IVIG period to 7.15 g/L, with a geometric mean ratio of 1.09. No patient had a serious bacterial infection during any part of the study. The annualized rate of infections, hospitalisations, days missed from school or work and antibiotic use were similar for the IVIG and SCIG periods.

INDICATIONS

Hizentra[®] is indicated in adults and children for replacement therapy in:

- Primary Immunodeficiency Disease (PID) and
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

CONTRAINDICATIONS

Hizentra[®] is contraindicated in patients with a history of severe systemic hypersensitivity or anaphylactic reactions/anaphylaxis to the active substance of Hizentra[®] or to any of its excipients.

Hizentra[®] must not be applied if any of the following listed conditions is existent:

- Hyperprolinaemia type I or II.

PRECAUTIONS

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 **Administration** should be adhered to. Patients should be closely monitored and carefully observed for any adverse events throughout the infusion period.

Hypersensitivity

Hypersensitivity reactions may occur even in patients who had tolerated previous treatment with human normal immunoglobulin.

Severe hypersensitivity or anaphylactic reactions up to shock can particularly occur in patients with known allergies to anti-IgA antibodies. 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.

In case of severe hypersensitivity/anaphylactic reactions the administration of Hizentra[®] must be stopped immediately. In case of shock, standard medical treatment should be administered.

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin, by initially injecting the product slowly
- 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.

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.

Embolic and thrombotic events

Arterial and venous thromboembolic events have been associated with the use of immunoglobulins. Caution should be taken in patients with pre-existing risk factors for thromboembolic events, such as advanced age, estrogen use, in-dwelling vascular catheters, a history of vascular disease or thrombotic episodes, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), patients with acquired or inherited hypercoagulable states, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity (including cryoglobulins, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies). In patients at risk for thromboembolic adverse reactions, Hizentra[®] should be administered subcutaneously at the minimum rate of infusion and dose practicable, and these individuals should be monitored for thrombotic complications. Consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity. Patients should be sufficiently hydrated before use of immunoglobulins.

Pathogen safety

Transmissible infective agents

Measures to prevent viral, bacterial, and fungal transmissible spongiform encephalopathy infections 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 these measures there remains the possibility that products derived from human plasma may contain pathogenic agents. Thus the risk of transmission of infectious agents cannot be totally eliminated. 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.

Effects on fertility

Animal fertility studies have not been conducted with Hizentra[®]. Based on clinical experience with immunoglobulins it is suggested that no harmful effects on fertility are to be expected.

Use in pregnancy

Animal reproduction studies have not been conducted with Hizentra[®]. 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 breastfeeding 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.

There was no evidence of a teratogenic effect of the excipient proline when administered to pregnant rats over the period of organogenesis.

Continued treatment of the pregnant woman ensures a passive immunity for the neonate.

Use in lactation

During breast-feeding immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Paediatric use

Hizentra[®] was evaluated in 46 paediatric patients (27 children [2 to 11 years] and 19 adolescents [12 to 16 years]) with primary immunodeficiency disease (PID). No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Clinical trials with Hizentra[®] showed a similar safety profile in paediatric and adult patients. The safety and efficacy of Hizentra[®] has not been formally studied in paediatric patients under two years of age.

Use in the elderly

Clinical studies included 6 patients over the age of 65. There were no elderly-specific dose requirements necessary to achieve the desired serum IgG levels.

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

Genotoxicity

No genotoxicity studies have been conducted with Hizentra[®]. The excipient proline was not genotoxic in a standard array of genotoxicity tests.

Carcinogenicity

No carcinogenicity studies have been conducted with Hizentra[®].

Effect on laboratory tests

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).

INTERACTIONS WITH OTHER MEDICINES

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. Refer to the Australian Immunisation Handbook for Australian clinical practice recommendations.

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

ADVERSE EFFECTS

Experience from clinical studies

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

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 (SOC) and frequency in **Table 2**. Frequency per infusion has been evaluated using the following criteria: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), and rare ($\geq 1/10,000$ to $< 1/1,000$).

Attachment 1: Product information for AusPAR Hizentra Normal Human Immunoglobulin CSL Behring Ltd 2013-00301-2-2 Final 25 June 2014. This Product Information was approved at the time this AusPAR was published.

Table 2: Adverse Reactions (ARs) Reporting Rate per Infusion, US & EU Phase I and Phase III Studies

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
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

Postmarketing Experience

In addition to the ADRs listed in **Table 2**, the following adverse reactions have been observed during post-approval use of Hizentra[®]:

Immune system disorders: anaphylactic reactions

Nervous system disorders: aseptic meningitis syndrome (AMS), tremor, burning sensation

Vascular disorders: thromboembolism

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.

Class Effects

Not known except infusion site reactions for subcutaneous immunoglobulin.

DOSAGE AND ADMINISTRATION

Hizentra[®] should only be administered **subcutaneously**.

Dosage

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

The dose regimen using the subcutaneous route should achieve a sustained level of IgG. A loading dose of at least 0.2 to 0.5 g/kg (1.0 to 2.5 mL/kg) body weight may be required. This may need to be divided over several days. After steady state IgG levels have been attained, maintenance doses are 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 dose is given by body weight and adjusted to the clinical outcome of the above mentioned conditions, the dose in the paediatric population is not considered to be different to that of adults. Likewise in the elderly, dosing should be determined by clinical response and guided by IgG trough levels.

Administration

NOTE: This product does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the vial. Use in one patient on one occasion only. Any unused solution should be discarded appropriately.

This product is normally clear and pale yellow or light brown. If it appears to be cloudy or contains particulate matter, do not use product but return the unopened vial to CSL Behring.

Hizentra[®] should only be administered **SUBCUTANEOUSLY. DO NOT ADMINISTER INTRAVENOUSLY.**

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

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. Injection sites should be at least 5 cm apart.

The recommended initial infusion rate depends on individual needs of the patient and should not exceed 15 mL/hour/site (see **PRECAUTIONS**). If well-tolerated, the infusion rate can then gradually be increased to 25 mL/hour/site.

Subcutaneous infusion for home treatment

If the supervising physician believes that home administration is appropriate, the patient or caregiver must be instructed in; subcutaneous administration techniques; the keeping of a treatment diary; recognition of and measures to be taken in case of severe adverse reactions.

OVERDOSAGE

Consequences of an overdose are not known. In case of overdosing the occurrence of adverse drug reactions should be closely monitored and, if necessary, supporting measures should be offered.

PRESENTATION AND STORAGE CONDITIONS

Hizentra[®] is presented as a 20% (20 g/100 mL) solution for subcutaneous administration. The solution is dispensed into a glass vial and closed with a rubber stopper and aluminium crimp cap, with a plastic flip off disc providing a tamper evident seal.

Attachment 1: Product information for AusPAR Hizentra Normal Human Immunoglobulin CSL Behring Ltd 2013-00301-2-2 Final 25 June 2014. This Product Information was approved at the time this AusPAR was published.

The product is supplied in the following pack sizes:

1 g in a 5 mL solution
2 g in a 10 mL solution
4 g in a 20 mL solution
10 g in a 50 mL solution

Store below 25°C (Do not freeze).

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

Do not use after the expiry date printed on the carton and the label.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

8 May 2014

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For Medical/Technical Enquiries

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