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1 PRODUCT NAME

Hizentra[®] (20% (20 g/100 mL)), solution for subcutaneous injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Normal Immunoglobulin

Hizentra[®] is a 20% solution containing 20 g/100 mL of 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 of normal human plasma (approximate values: 69% IgG₁, 26% IgG₂, 3% IgG₃, 2% IgG₄).

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

Hizentra[®] 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.

3 PHARMACEUTICAL FORM

Hizentra[®] is a clear and colourless or pale-yellow or light-brown solution for subcutaneous injection.

Hizentra[®] has a nominal osmolality of 380 mOsm/kg and is approximately isotonic. The pH value of the ready-to-use solution is 4.8.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults and children in:

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

Immunomodulatory therapy:

- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as maintenance therapy in adults and children to prevent relapse of neuromuscular disability and impairment.

4.2 Dose and method of administration

Dose

The dose and dose regimen are dependent on the indication.

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.

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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 (bw) 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, from daily to once every two weeks, to reach a cumulative monthly dose of the order of 0.4 to 0.8 g/kg (2.0 to 4.0 mL/kg) bw. 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 patients

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 bw per week. The initial subcutaneous dose may be a 1:1 conversion from the previous IVIg dose (calculated as weekly dose) but should not be less than 0.2 g/kg bw per week. The weekly dose can be divided into smaller doses and administered by the 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. The patient's individual clinical response should be the primary consideration in dose adjustment.

Elderly

The dose in the elderly population is not considered to be different from that in patients 18 to 65 years of age as the dose is given by body weight and adjusted to the clinical outcome.

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.

Paediatric population

As the dose is given by body weight and adjusted to the clinical outcome of the above mentioned conditions the dosage regimen is the same in the paediatric population as in adults.

Hizentra[®] was evaluated in 68 paediatric patients with PID aged 2 to <12 years and in 57 adolescents aged 12 to <18 years. No paediatric-specific dose adjustments were necessary to achieve the desired serum levels.

Hizentra[®] was not evaluated in clinical studies in paediatric patients with CIDP who are under the age of 18.

Method of administration

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

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Hizentra[®] may be infused into sites such as abdomen, thigh, upper arm, and / or lateral hip. If large doses are given (>50 mL), it may be advisable to administer the dose at multiple sites. There is no limit to the number of infusion sites administered in parallel. More than one infusion device can be used simultaneously. The volume of product infused into a particular site may vary. Infusion sites should be at least 5 cm apart.

Hizentra[®] can be infused using:

- an infusion device or
- by manual push with a syringe.

Infusion rate

The recommended 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, the infusion rate can be further increased as per patient's individual tolerability.

Manual push infusion

The recommended initial infusion rate should not exceed 0.5 mL/min (30 mL/hour/site).

If well-tolerated, the infusion rate can be increased up to 2.0 mL/min/site (120 mL/hour/site), based on the healthcare professional's judgement and patient's individual tolerability.

Table 1: Times for infusion by manual push depending on the infusion rate:

Infusion rate Syringe volume	0.5 mL/min/site (30 mL/hour/site)	1 mL/min/site (60 mL/hour/site)	2 mL/min/site (120 mL/hour/site)
5 mL	10 min	5 min	2.5 min
10 mL	20 min	10 min	5 min
20 mL	40 min	20 min	10 min

It is recommended to use needles gauge 24 or larger (i.e. lower gauge number). 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 at a time. Do not reuse the needle.

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.

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4.3 Contraindications

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

Hizentra[®] is contraindicated in patients with hyperprolinaemia type I or II.

4.4 Special warnings and precautions for use

Route of administration

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

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

Hypersensitivity / Anaphylaxis

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.

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 hypovolaemic patients, patients with diseases which increase blood viscosity (including cryoglobulins, fasting chylomicronaemia 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

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measurement of baseline blood viscosity in individuals at risk for hyperviscosity. 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 IgG 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 cerebrospinal fluid studies, to rule out other causes of meningitis. Discontinuation of IgG treatment may result in remission of AMS within several days without sequelae.

Pathogen safety

Hizentra[®] is made from human plasma. 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 Hizentra[®] and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is recommended that every time Hizentra[®] is administered to a patient, the name and batch number of Hizentra[®] are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicines 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. Refer to the Immunisation Handbook for clinical practice recommendations.

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.

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

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.

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.

Breast-feeding

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

Fertility

Based on clinical experience with immunoglobulins it is suggested 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 the safety profile

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

The ADRs have been collected in Hizentra[®] clinical trials from 7 phase III studies in patients with PID (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).

The ADRs reported in these clinical studies are summarised and categorised according to the MedDRA System Organ Class (SOC) and Preferred Term (PT) level. The frequency per patient and per infusion has been evaluated using the following criteria: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$). For spontaneous post-marketing ADRs, the reporting frequency is categorised as unknown.

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Table 2: Adverse Drug Reactions (ADRs) Associated with Hizentra® Obtained from Clinical Studies and Post-marketing Surveillance, Reporting Rate per Patient and per Infusion

MedDRA System Organ Class	ADR MedDRA Term	ADR frequency category	
		Per Patient	Per Infusion
Infections and infestations	Nasopharyngitis	Very common	Uncommon
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

Safety profile of higher infusion volumes per site and higher infusion rates in manual push and pump-assisted administration techniques

In the study assessing the safety and tolerability of higher infusion volumes per site and higher infusion rates applied via the manual push and pump-assisted administration, a total of 49 PID patients were enrolled into the corresponding 3 groups (see section 5.1 Pharmacodynamic effects). There were no clinically relevant differences in the frequency, type, or intensity of adverse events among the 3 groups. The most frequent adverse events were local site reactions of mild or moderate intensity. The number, type, intensity, or duration of local site reactions did not increase with an increasing infusion parameter in any of the study cohorts. No relevant differences were observed between the BMI \geq / $<$ 30 kg/m² (n = 14) and age ($>$ / $<$ 18 years) sub-groups. Pump infusion rates up to 100 mL/hour/site, infusion volumes up to 50 mL/site and manual push administration with flow rates up to 2.0 mL/min/site (120 mL/hour/site) were well-tolerated. The safety profile was similar to that of previous PID studies.

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Class effects

Infusion site reactions for SCIg.

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

Information available from 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hizentra[®] contains functionally intact IgG with a broad spectrum of antibodies against infectious agents. It has a distribution of IgG subclasses closely proportional to that in native human plasma. The Fc and Fab functions of the IgG molecule are retained.

Hizentra[®] contains the IgG antibodies present in the normal population. It is prepared from plasma from 1000 or more human donors. 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.

Mechanism of action

This medicine supplies a broad spectrum of opsonising and neutralising IgG antibodies against a wide variety of bacterial and viral agents. In immunodeficiency, adequate doses of Hizentra[®] may restore abnormally low IgG antibody levels to the normal range and thus help against infections.

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The mechanism of action in CIDP is not fully understood, but may include immunomodulatory effects.

Clinical efficacy and safety

The safety and efficacy of Hizentra[®] has been assessed in 7 phase III studies and 2 phase IV studies in patients with PID, and in 1 phase III study including 1 extension study in patients with CIDP.

Primary Immunodeficiency Diseases (PID)

In the prospective, open-label, multicentre, single-arm European study, a total of 51 subjects aged between 3 and 60 years were enrolled from previous treatment with intravenous immunoglobulin (IVIg) (60.9%) or subcutaneous immunoglobulin (SCIg) (39.1%) and switched to Hizentra[®]. The objectives of the study were to investigate the efficacy, tolerability, safety, pharmacokinetics, and health-related quality of life (HRQL) 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 bw, 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 intention-to-treat 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 hospitalised 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 score. No differences were observed for Hizentra[®] compared to previous SCIg treatment.

In the US a prospective, open-label, multicentre, 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 population. The primary endpoint was annual rate of SBIs per subject.

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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%). Twelve 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 hospitalised 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, HRQL, pharmacoeconomics and PK of Hizentra[®] in subjects with PID.

Twenty-five 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 bw. 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 annualised rate of infections, hospitalisations, days missed from school or work and antibiotic use were similar for the IVIg and SCIG periods.

To assess the safety and tolerability of higher infusion rates applied via the manual push and pump-assisted administration technique, 49 PID subjects aged 2 to 75 years were enrolled in an open-label, multicentre, parallel-arm, nonrandomised phase IV 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 patient group (n = 16) receiving Hizentra[®] via the manual push technique (manual push flow rate cohort), 2 to 7 infusions per week were administered with the flow rates of 25–30, 60 and 120 mL/hour/site corresponding to 0.5 mL/min, 1.0 mL/min or 2.0 mL/min per site (30, 60 or 120 mL/hour/site). In the patient group (n = 18) receiving Hizentra[®] via pump-assisted administration (pump-assisted flow rate cohort), weekly Hizentra[®] infusions were administered with 25, 50, 75 and 100 mL/hour/site flow rate. In addition, higher infusion volumes of 25, 40 and 50 mL per site (pump-assisted volume cohort) were evaluated in pump-assisted administration of weekly

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Hizentra[®] doses (n = 15). In all three groups, each infusion parameter was used for 4 weeks, after which tolerating subjects could switch to the next higher infusion parameter.

Overall, the tolerability* was ≥ 0.98 for all infusion parameter levels in all cohorts. The percentage of subjects responding to a higher infusion parameter (= responder**) was: in the manual push flow rate cohort 100.0% at the 30 mL/hour and 60 mL/hour, and 87.5% at the 120 mL/hour per site; in the pump-assisted flow rate cohort 77.8% at the 25 mL/hour and the 50 mL/hour, 66.7% at the 75 mL/hour, and 61.1% at the 100 mL/hour per site; in the pump-assisted volume cohort 86.7% at the 25 mL and 73.3% at the 40 mL and 50 mL per site. No clinically relevant differences in the serum IgG trough concentrations were observed between the baseline at day 1 and at the end of the study in all subjects.

*Tolerability: number of infusions without severe local reactions divided by the total number of infusions

**Responder:

Pump-assisted cohorts: a subject who performed ≥ 3 valid infusions out of 4 for an infusion parameter.

Manual push flow rate cohort: a subject who performed the minimum number of valid infusions ($\geq 60\%$) for an infusion parameter level.

An infusion rate was considered valid, if $\geq 95\%$ of the planned flow rate/volume per ≥ 1 infusion site was achieved.

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.

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.

Chronic Inflammatory Demyelinating Polyneuropathy (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 subjects previously treated with 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).

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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 was evaluated, and the corresponding probabilities for CIDP relapse based on Kaplan-Meier estimates were: placebo, 58.8%; 0.2 g/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 in any of the measurements.

In the efficacy scores (INCAT score, mean grip strength, and Medical Research Council (MRC) 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 0.2 g/kg and 0.4 g/kg bw weekly doses.

Due to the design of the extension study, some patients switched dosing from 0.2 g/kg bw to 0.4 g/kg bw, or vice versa during the study. For this reason 72/82 subjects received doses of 0.4 g/kg and 73/82 subjects received doses of 0.2 g/kg during the safety and efficacy evaluation period. The mean efficacy evaluation period for the extension study 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 received 0.4g/kg bw from enrolment for up to 24 weeks in the extension study had a relapse rate of 5.6% (1/18 patients). For all patients who received 0.4 g/kg bw at some point 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), however, the patient cohort was small. For all patients who received 0.2 g/kg bw at some point in the extension study, 47.9% (35/73 patients) had a relapse, with a median time to first relapse of 215.0 days. Down-titrating

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patients in the extension study from 0.4 g/kg to 0.2 g/kg bw dose without occurrence of relapse was possible in 67.9% of subjects (19/28 patients); all 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

Hizentra[®] was not 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 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 to 3 days.

Elimination

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

Primary Immunodeficiency Disease (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.

The pharmacokinetics were evaluated in a subset of 23 subjects with Primary Immunodeficiency (PID) (refer to **Table 3**).

Table 3: Steady state pharmacokinetic parameters of Hizentra[®] in 23 PID patients

Parameter	Pivotal EU study
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 concentration–time curve during regular dosing interval.

SD: standard deviation.

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Simulations with empirical population-pharmacokinetic models suggested that a comparable IgG exposure (C_{max} , $AUC_{0-14 \text{ days}}$, $C_{min, 14 \text{ days}}$) is achieved when Hizentra[®] is administered subcutaneously every two weeks using double the weekly dose during maintenance therapy. These simulations further suggested that a comparable IgG exposure is 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 $\leq 4\%$ 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.

In a phase IV study evaluating higher Hizentra[®] infusion parameters in manual push and pump-assisted administration, serum IgG trough levels were measured in 49 PID subjects at the end of study versus baseline at day 1 after enrolment. No clinically relevant differences in the serum IgG trough concentrations were observed between the baseline at day 1 and at the end of the study.

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.

Chronic Inflammatory Demyelinating Polyneuropathy (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 24 weeks of Hizentra[®] treatment in the 0.4 g/kg bw group was 20.6 (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 (C_{max} , $AUC_{0-14 \text{ days}}$, $C_{min, 14 \text{ days}}$) 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 patient population.

Paediatric population

Hizentra[®] was not evaluated in clinical studies in paediatric patients with CIDP who were 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.

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5.3 Preclinical safety data

IgG are normal constituents of the human body. 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 proline. Non-clinical data revealed no special risk for humans based on safety pharmacology and toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Shelf life after opening:

Use in one patient on one occasion only. Hizentra[®] should be administered as soon as possible after opening the vial / pre-filled syringe as the solution contains no preservative.

6.4 Special precautions for storage

Store below 25°C (Do not freeze).

Keep the vial or the pre-filled syringe in the outer carton in order to protect from light.

For storage conditions after first opening of Hizentra[®], see section 6.3.

6.5 Nature and contents of container

Hizentra[®] is provided as a 20% (20 g/100 mL) ready-to-use solution for subcutaneous administration in single-use vials or single-use pre-filled syringes.

- 5, 10 or 20 mL of solution in a vial (type I glass), 50 mL of solution in a vial (type II glass), with a stopper (halobutyl), a cap (aluminium crimp) and a flip off disc (plastic).
- 5, 10 or 20 mL of solution in a pre-filled syringe (cyclo-olefin-copolymer (COC)). The syringe is packed in a blister that includes an oxygen absorber sachet.

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Pack sizes:

- One vial of 5 mL solution containing 1 g human normal immunoglobulin.
- One vial of 10 mL solution containing 2 g human normal immunoglobulin.
- One vial of 20 mL solution containing 4 g human normal immunoglobulin.
- One vial of 50 mL solution containing 10 g human normal immunoglobulin.
- One pre-filled syringe of 5 mL solution containing 1 g human normal immunoglobulin.
- One pre-filled syringe of 10 mL solution containing 2 g human normal immunoglobulin.
- One pre-filled syringe of 20 mL solution containing 4 g human normal immunoglobulin.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Hizentra[®] should be at room temperature before use. Do not shake the Hizentra[®] vial or pre-filled syringe.

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 or pre-filled syringe to CSL Behring.

Any unused solution should be discarded appropriately.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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10 DATE OF REVISION OF THE TEXT

10 January 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.5	Addition of 20 mL pre-filled syringe