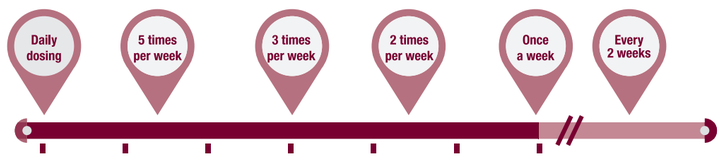
Hizentra flexibility to suit individual patient lifestyles[1]*



- Approved flexible administration daily to once every two weeks[1]
- With no upper limit, you can now determine an infusion rate based on individual patient tolerability[1**]
- The only SCIg licensed for CIDP[1]
- The only SCIg licensed for storage at room temperature for 30 months[1]
- Proven to protect PID patients from serious bacterial infection[4]

* Hizentra Summary of Product Characteristics (SPC), updated on 20th March 2018.

** Initial infusion rate is 15 ml/hr/site. Subsequent two infusions, rate can be increased gradually to 25 ml/hr/site. In adults, doses over 30 ml may be divided according to patient preference and in infants and children, the infusion site may be changed every 5-15 ml.
Maximum infusion rate may be determined by pump type, if used.

PRESCRIBING INFORMATION
(Please refer to the Summary of Product Characteristics before prescribing)

Hizentra® (Human normal immunoglobulin (SCIg) 200mg/ml for subcutaneous injection).
Indications: Replacement therapy in adults, children and adolescents (0-18 years) in primary immunodeficiency syndromes with impaired antibody production. Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated; hypogammaglobulinaemia and recurrent infections in multiple myeloma (MM) patients; hypogammaglobulinaemia in patients pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT). Immunomodulatory therapy in adults, children and adolescents (0-18 years) in the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg.

Dosage and method of administration:
The dose and dose regimen are dependent on the indication.

Posology – Adults and children (0-18 years):
Replacement Therapy
Adults and children (0-18 years): The dose may need to be individualised dependent on the pharmacokinetics (see section 5.2 of SmPC), clinical response and IgG trough levels. A loading dose of at least 0.2-0.5g/kg (1-2.5ml/kg) bodyweight – divided over several days. Maintenance doses are given at repeated intervals to reach a cumulative monthly dose of about 0.4 to 0.8 g/kg (2-4ml/kg) bodyweight. Assess trough IgG levels in conjunction with clinical response to adjust dose and/or dose interval to achieve higher trough levels.

Immunomodulatory therapy in CIDP patients
The dose may need to be individualised dependent on the pharmacokinetics (see section 5.2 of SmPC), clinical response and IgG trough levels. The therapy with Hizentra is initiated 1 week after the last IVIg infusion. The recommended subcutaneous dose is 0.2 to 0.4 g/kg body weight per week. The initial subcutaneous dose may be a 1:1 conversion from the previous IVIg dose (calculated as weekly dose). The weekly dose can be divided into smaller doses and administered by desired number of times per week. For dosing every two weeks, double the weekly Hizentra dose. The dose may need to be adapted to achieve the desired clinical response. Patient`s individual clinical response should be the primary consideration in dose adjustment. In case of clinical deterioration the dose may be increased to the recommended maximum of 0.4g/kg weekly dose. Hizentra maintenance therapy in CIDP has not been studied for periods longer than 6 months. Individualise the duration of any treatment beyond 6 months based upon the patient's response and demonstrated need for continued therapy. Direct comparative data for Hizentra versus IVIg are not available. Please refer also to section 5.1. Hizentra has not been evaluated in clinical studies in paediatric patients with CIDP who are under the age of 18.
Administration
Administer via the subcutaneous route. Initial infusion rate should not exceed 20ml/hour/site and can increase to 35ml/hour/site for the following two infusions if well-tolerated. Thereafter, the infusion rate can be increased further as per patient's tolerability. More than one infusion device can be used simultaneously. The amount of product infused into a particular site may vary. In infants and children, infusion site may be changed every 5-15 ml. In adults, doses up to 50 ml may be given. There is no limit to the number of infusion sites. Infusion sites should be at least 5 cm apart.
Contraindications: Hypersensitivity to any of the components of the product, hyperprolinaemia (type I or II), **Hizentra must not be given intravascularly** .
Special warnings and special precautions for use: Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the product is switched or when treatment has been interrupted for more than eight weeks. These patients should be monitored during the first infusion and for the first hour thereafter, to detect potential adverse reactions. Observe all other patients for at least 20 minutes after administration. Potential complications can often be avoided by ensuring patients are not sensitive to human normal immunoglobulin, by first infusing the product slowly and monitoring patients carefully for any symptoms throughout the infusion period. Discontinue immediately on suspicion of an allergic or anaphylactic reaction. In case of shock, standard medical treatment should be applied.
Hypersensitivity: True hypersensitivity reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with caution. Only use Hizentra in these patients under close medical supervision. Rarely, a fall in blood pressure with anaphylactic reaction can occur, even in patients who had tolerated previous treatment with normal human immunoglobulin.
Thromboembolism: Caution should be exercised in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severely hypovolemic disorders, diseases which increase blood viscosity). Patients should be sufficiently hydrated before use.
Aseptic meningitis (AMS): AMS has been reported with use of IVIg or SCIg
Hizentra is essentially sodium free
Safety with respect to transmissible agents: Despite standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma, the possibility of transmitting infective agents cannot be totally excluded. The measures are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses, HAV and parvovirus B19.
Effects on ability to drive and use machines: The ability to drive and operate machines may be impaired by some adverse reactions associated with Hizentra.
Undesirable effects: Chills, headache, migraine, fever, vomiting, allergic reactions, nasopharyngitis, hypertension, diarrhroea, nausea, arthralgia, low blood pressure, chest pain, abdominal pain, musculoskeletal pain), including arthritis, muscle spasms and muscular weakness, tremor including psychomotor hyperactivity, pruritus and moderate low back pain. Local reactions at infusion sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash. Rarely human immmunoglobulins 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. Adverse reactions reported during post- approval use: anaphylactic reactions, aseptic meningitis syndrome, lethargy, tremor, burning sensation, thromboembolism, infusion site ulcer. Please refer to the Summary of Product Characteristics for further information and a list of rare reactions.
Legal Category: POM. **Date text last revised:** 05 Mar 2018.
Marketing Authorisation Holder: CSL Behring GmbH, Emil-von-Behring-Strasse 76, D35041 Marburg Germany
Marketing Authorisation Number: EU/1/11/687/001-006, 010-012.

For a copy of the SmPC or further medical information, please contact medical@dccvital.com.
Adverse events should be reported to Fannin Ltd, Pharmacovigilance at +353 86 8394447 or medical@dccvital.com
Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 1 676 4971; Fax: +353 1 676 2517. Website: www.hpra.ie; Email: medsafety@hpra.ie

IE/18/001/SmPC-Mar 2018

References:
1. Hizentra Summary of Product Characteristics. **2.** Sidhu J, Rojavin M, Pfister M, Edelman J. Enhancing patient flexibility of subcutaneous immunoglobulin G dosing: pharmacokinetic outcomes of various maintenance and loading regimens in the treatment of primary immunodeficiency. Biol Ther. 2014 Aug 14. **3.** Richter A. Frequent SCIG push in clinical practice. Abstract Book Antibody Deficiency: Flexible IgG Dosing and Management of Autoimmune Disease: 16th Biennial Meeting of the European Society for Immunodeficiencies (ESID 2014), Prague, Czech Republic, 29 October–1 November, 2014. **4.** Jolles S, et al. Efficacy and safety of Hizentra® in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clin Immunol. 2011;141:90-102.

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CSL Behring
Biotherapies for Life™

Biotherapies for Life™ CSL Behring

Updated dosing information inside[1]

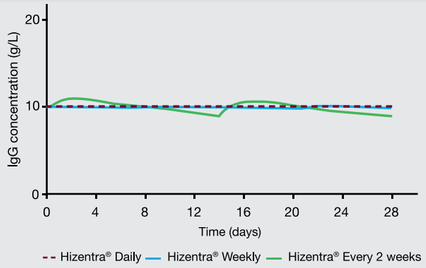
Flexible administration for individualised therapy

Abbreviated Prescribing Information can be found on the back page.

Hizentra®
Human Normal Immunoglobulin (SCIg)
200 mg/ml solution for subcutaneous injection

Flexible administration of Hizentra provides comparable serum IgG levels

Median serum IgG levels following Hizentra® daily, weeky, and every 2 weeks administration[2]



Pharmacokinetic simulations comparing the steady-state concentration-time profiles of plasma IgG following daily, weekly, and every 2 weeks subcutaneous immunoglobulin (SCIg) administration with Hizentra® show similar systemic exposure.

Adapted from Sidhu J et al 2014 Based on pharmacokinetic modelling and simulations

Consider the freedom of Hizentra

- Training time up to 2.5 hours[3]
- No cost for pumps, batteries or maintenance
- Planned holidays can be accommodated, missed doses replaced

* Subcutaneous 'manual push' injection

Hizentra®
Human Normal Immunoglobulin (SCIg)
200 mg/ml solution for subcutaneous injection