14 October 2021
EMA/618177/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hizentra

International non-proprietary name: human normal immunoglobulin

Procedure No. EMEA/H/C/002127/II/0129

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Abbreviated Term
AE	Adverse event
CLL	Chronic lymphocytic leukemia
Ctrough	IgG trough concentration level
EMA	European Medicines Agency
EU	European Union
HSCT	Hematopoietic stem cell transplant
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgRT	Immunoglobulin replacement therapy
IV	Intravenous
IVIG	Intravenous immunoglobulin
MM	multiple myeloma
NHL	Non-Hodgkin’s Lymphoma
PID	Primary immunodeficiency
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SBI	Serious bacterial infections
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SID	Secondary immunodeficiency

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, CSL Behring GmbH submitted to the European Medicines Agency on 7 April 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to expand the approved secondary immunodeficiencies (SID) indications to any symptomatic SID in accordance with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/ 2007 Rev 5; CHMP, 2018). As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.6 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	7 April 2021

Timetable	Actual dates
Start of procedure:	24 April 2021
CHMP Rapporteur Assessment Report	18 June 2021
PRAC Rapporteur Assessment Report	25 June 2021
PRAC members comments	30 June 2021
PRAC Outcome	8 July 2021
CHMP members comments	12 July 2021
Request for supplementary information (RSI)	22 July 2021
CHMP Rapporteur Assessment Report	01 September 2021
PRAC Rapporteur Assessment Report	01 September 2021
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	30 September 2021
CHMP members comments	N/A
Updated CHMP Rapporteur Assessment Report	N/A
Opinion	14 October 2021

2. Scientific discussion

2.1. Introduction

In the updated EMA core SmPC for **IVIGs** EMA/CHMP/BPWP/94038/2007 Rev. 5 (effective as of 1st January 2019) the indication for SID is as follows

- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l

  * PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

This indication is not yet part of the coreSmPC for SCIGs

2.1.1. Problem statement

As outlined above, in 2019 the SID indication in the coreSmPC for IVIGs was expanded from CLL, MM, and HSCT to encompass other entities that could lead to a secondary immunodeficiency, whilst also providing a clearer outline of what constitutes an antibody deficiency in this setting. As many patients with SIDs require prolonged treatment with Igs, it may prove beneficial to provide SCIG home treatment for these patients.

The Marketing Authorisation Holder (MAH) has provided literature both with their product Hizentra and from the class of SCIGs and IVIGs in support of this extension/modification of indication.

Disease or condition

SID is an umbrella term for variety of diseases with secondary immune defects, including hematologic malignancies, HIV infections, prematurity, hypogammaglobulinemia associated with solid organ or bone marrow transplantation. Medications such as rituximab, CD19-targeting agents, CAR-T cell therapy, penicillamine, atacicept, imatinib, cyclophosphamide, anticonvulsant and antiepileptic drugs, mycophenolate mofetil, corticosteroids, sulphasalazine, and gold can result in SID. Secondary antibody deficiencies, a humoral type of SID, can be up to 30 times more common than primary immunodeficiencies [Patel et al, 2019].

Currently, SID indications approved for IgPro20 and other SCIG products in the EU are limited to CLL, MM, and Hematopoietic stem cell transplant (HSCT).

Similar to PID, SID can often manifest as increased frequency or unusual complications of common infections [Chinen and Shearer, 2010] and can benefit from IgG immune-replacement therapy in the same range of recommended doses regardless of the underlying cause, with adjustment to the individual response to treatment. However, unlike PID, SID can be reversible if the underlying cause is resolved.

State the claimed the therapeutic indication

In analogy to IVIG the claimed SID indication for Hizentra would be:

Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of < 4 g/l.

***PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.**

Dosing for replacement therapy in PID/SID:

The dose regimen should achieve a trough level of IgG level (measured before the next infusion) of at least 6 g/l within the normal reference range for the population age. A loading dose of at least 0.2 to 0.5 g/kg (1.0 to 2.5 ml/kg) body weight may be required. This may need to be divided over several days. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4 to 0.8 g/kg (2.0 to 4.0 ml/kg) body weight. Each single dose may need to be injected at different anatomic sites.

Trough levels should be measured and assessed in conjunction with the patient's clinical response. Depending on the clinical response (e.g., infection rate), adjustment of the dose and/or the dose interval may be considered in order to aim for higher trough levels.

Infusion volumes and rates

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, if the patient tolerates the initial infusions at the full dose per site and maximum rate, an increase in the infusion rate of successive infusions may be considered at the discretion of the patient and based on the healthcare professionals' judgement.

Manual push infusion

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

If well-tolerated, the infusion rate can be increased up to 2.0 ml/min/site (120 ml/hour/site). Thereafter, if the patient tolerates the initial infusions at the full dose per site and maximum rate, an increase in the infusion rate of successive infusions may be considered at the discretion of the patient and based on the healthcare professionals' judgement.

A 24 or larger (i.e., lower gauge number) needle gauge may be required to allow patients to infuse at higher flow rates. 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. If administration with an additional Hizentra syringe is required, a new sterile injection needle should be used, and the infusion site changed.

Epidemiology

The epidemiology is difficult to assess as the umbrella term SID covers a wide range of underlying disorders. Here are some of the main categories:

Chronic lymphocytic leukemia (CLL) worldwide (ww) incidence: 1-5.5 /100.000

Multiple myeloma (MM) ww incidence: 0.5 – 5.3/100.000

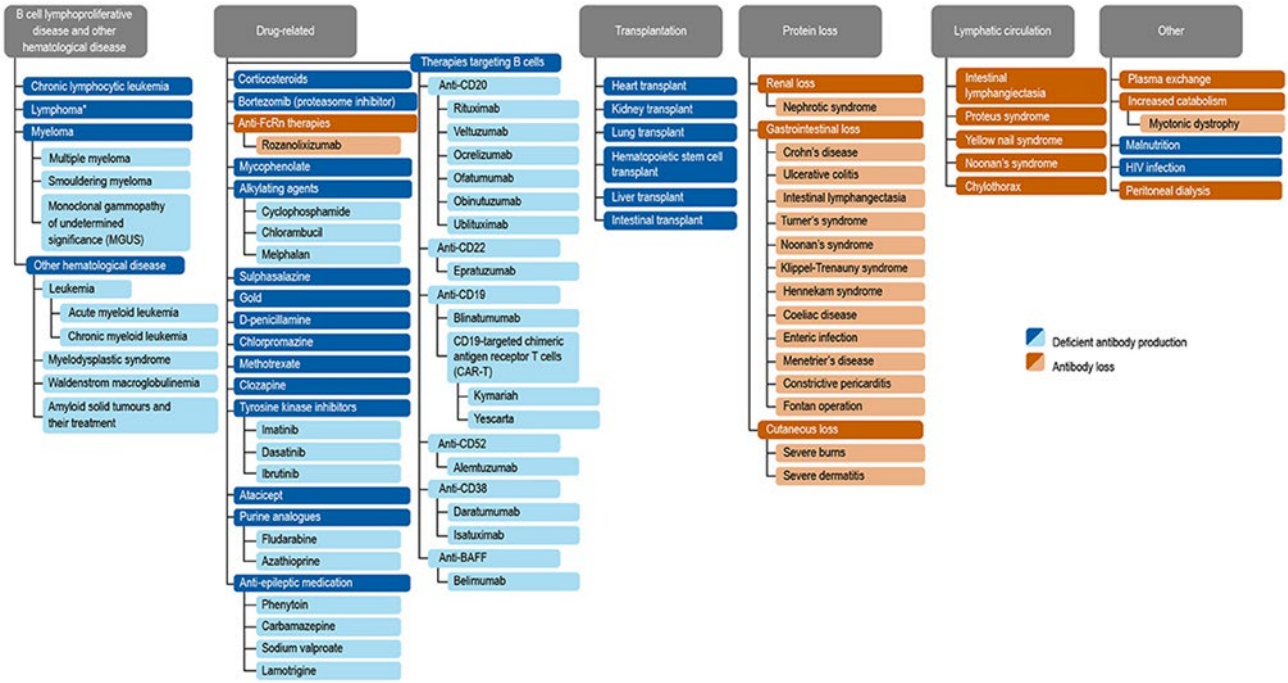
Hematopoietic stem cell transplant (HSCT) in EU in 2017: 30.000 cases

Solid organ transplantation (SOT) ww in 2014: 119.873

Aetiology and pathogenesis

See also "Disease or condition"

Figure 1. Common causes of secondary deficiency



Frontiers | The Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management | Immunology (frontiersin.org) [Patel et al, 2019].

Clinical presentation, diagnosis, and prognosis

Relevant in the context of this Variation Procedure is the aspect that in a number of SIDs with antibody depletion/deficiency the clinical presentation (and thus treatment) is similar to PIDs.

In CLL up to 80% of CLL patients experience infectious complications at some point during their disease, 20% of them severe/major infections. Up to 60% of overall mortality in CLL is caused by infectious complications.

In a study of more than 3,000 patients with multiple myeloma, infections were responsible for 45% of deaths within 6 months of diagnosis (SID - Secondary Immune Deficiency in Haematologic Malignancies » SID (secondaryimmunodeficiency.com)

Management

Currently, treatment of primary diseases that cause SID includes antibiotics, steroids, chemotherapy, monoclonal antibodies, and immunoglobulin replacement therapy (IgRT). Protocols for IgRT in secondary antibody deficiency vary, and a 12-month use of IgRT (with infection monitoring) is recommended in case of antibody failure and a lack of an adequate response to prophylactic antibiotics

in association with a significant ongoing infection burden [Jolles et al, 2017]. Currently, IgRT is administered via either IVIG or SCIG routes [Perez et al, 2017]

Prophylactic non-live vaccinations such as influenza are recommended for patients with SID. Live vaccination is generally not recommended. Use of inactivated vaccines in patients with MM is allowed, unless they are actively receiving chemotherapy or monoclonal antibody therapy

Recent market research of secondary specialty pharmacy data from the United States, France, the United Kingdom, Germany, Spain, Australia and Canada reported that the major secondary antibody deficiency indications leading to IgRT usage were CLL and MM, which represent **39.2–54.9% of all patients with secondary antibody deficiency receiving IgRT**.

To extend the indication beyond the use of CLL and MM (which represent ~39 –55% of all patients with SID receiving IgRT) to encompass the suggested broader indication of SID, an increase in demand would be imminently expected.

2.1.2. About the product

IgPro20 (HIZENTRA) is a 20% ready-to-use liquid formulation of polyvalent human immunoglobulin G (IgG) for SC administration produced by CSL Behring. The IgG portion represents all IgG subclasses present in human plasma. IgG function (fragment crystallizable region and antigen binding fragment mediated activity) is retained. The sterile 20% IgG solution is stabilized with 250 mmol/L L-proline at pH 4.8. IgPro20 also contains 8 to 30 mg/L polysorbate 80. It has a low sodium content (< 10 mmol/L), with an osmolality of approximately 390 mOsmol/kg, and does not contain any preservatives. The protein moiety of IgPro20 is highly purified IgG (≥ 98% purity). More than 90% of the IgG consists of monomers and dimers. IgPro20 is prepared from large donor pools and represents the antibody spectrum present in the donor population. The manufacturing process of the subcutaneous immunoglobulin (SCIG) solution Hizentra is based on the IgPro10 (Privigen: EMEA/H/C/831) process except for formulation and final protein concentration. Filling sizes include 5 mL (1 g), 10 mL (2 g), 15 mL (3 g) and 20 mL (4 g).

IgPro20 (marketed as Hizentra®) is a Human Normal Immunoglobulin product that belongs to the pharmacotherapeutic group of immune sera and immunoglobulins (Anatomical Therapeutic Chemical classification code: J06BA01): immunoglobulins, normal human, for extravascular (subcutaneous [SC]) administration. It is approved for replacement therapy in primary immunodeficiency (PID) and various other indications and has been marketed in many countries including the United States (US), the European Union (EU), Canada, Switzerland, Japan, and Australia. Currently, secondary immunodeficiency (SID) conditions approved by European Medicines Agency (EMA) for IgPro20 are limited to chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and hematopoietic stem cell transplant (HSCT).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No Scientific Advice was sought. But as the indication requested in this Variation Procedure is already an accepted indication in the coreSmPC for IVIGs, where no further studies are required for the Variation of the SID indication wording (apart from a PID study for the initial MAA). It is acceptable to use the IVIG coreSmPC as a basis for the approach to including the SID wording for an SCIG product, provided the questions posed are satisfactorily answered.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

There are no changes to the risks of the product for the environment in relation to this application.

2.2.2. Conclusion on the non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

The updated data submitted in this application and the new/extended indication does not lead to a significant increase in environmental exposure further to the use of human normal immunoglobulin.

- Considering the above data, human normal immunoglobulin is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The Variation Application is based on literature studies either with Hizentra (IgPro20) or other SCIGs and/or IVIGs in the indication of SID.

As SCIGs can be viewed as a class of biologics that have shown similar efficacy in the PID setting and for CLL and MM, it is acceptable to base this application on a literature review, provided that sufficient data is evaluable for Hizentra in SID patients. Furthermore, any data from IVIG/SCIG studies in SID is considered supportive. Data from the various studies may also inform on dosing, keeping in mind that in immunoglobulin replacement therapy (IgRT) should be tailored to the individual patient's needs. Data on safety in the SID setting should be assessed against the backdrop of Hizentra's safety profile to date.

GCP

The MAH has provided a statement on the literature studies and their accordance with the ethical standards of Directive 2001/20/EC.

2.4. Clinical efficacy

2.4.1. Main studies

The MAH has provided a tabular overview of studies and their outcome in SID either with SCIGs or/and IVIGs

(N.B. this has been modified by the assessor not to include the studies with only IVIG and also to omit individual case reports).

Table 1. Tabular overview of clinical studies

Title (Reference)	Study Duration Number, Age, and Gender of Subjects	Major Inclusion/ exclusion Criteria	Efficacy and Safety Endpoints	Efficacy and Safety Results
SCIG				
[Vacca et al, 2018] Single centre, Italy Prospective, randomised, controlled study (SCIG vs no SCIG) IgPro20 (20%) 0.4 to 0.8 g/kg SCIG, divided into 4 weekly doses	Study duration: 18 months of SCIG infusions (range 10 to 28 months) N = 46 Age of participants: Mean 71 years Gender: 54% male	Inclusion: confirmed MM (CRAB criteria), >18 years old, serum IgG <500 mg/dL, life expectancy >1 year, verified ability to infuse SCIG at home, informed consent Exclusion: Other causes of immunodeficiency, active HCV and / or HBV or HIV, difficulties with home-based infusion	Efficacy: Annual rate of severe infections, days hospitalised, days under antibiotics, improved HRQoL Safety: AEs	Efficacy: Significantly lower number of infections ($p < 0.001$) in the SCIG group ($p < 0.01$). Lower incidence of total ($p < 0.001$) and severe ($p < 0.01$) infections Mean hospitalisation due to severe infections was 8 days for SCIG vs 121 for control group ($p < 0.001$) Mean days of antibiotic use were 28 for SCIG and 217 for controls ($p < 0.001$) SCIG patients improved QoL Safety: Low grade AEs, only 3 grade 3 / 4 which resulted in SCIG withdrawal (allergic skin reaction, pain)
[Dimou et al, 2018] Single centre, Greece Retrospective study Facilitated SCIG (conc. not specified) 0.4 to 0.8 mg/kg/month	Study duration: 2015 to 2018 N = 33 Age of participants: Not stated Gender: Not stated	Inclusion: hypogammaglobulinemia due to haematological malignancies treated with SCIG Exclusion: Not stated	Efficacy: Number of infections Safety: Adverse drug reactions	Efficacy: 18% of patients presented with ≥ 1 infections episode during SCIG treatment (all patients had IgG levels ≤ 6 g/L at the time of infection) Safety: 9% presented with ADRs after SCIG administration (fever and headache)
[Compagno et al, 2014a] Single centre, Italy Retrospective study Subcuvia (conc. not specified) or IgPro20 (20%) Mean dose 75 mg/week	Study duration: Not stated N = 61 Age of participants: 67% > 65 years old Gender: 57% male	Inclusion: IgG <6g/L with non-neutropenic infections requiring antibiotics Exclusion: Not stated	Efficacy: IgG levels Infections from patient diary Safety: Ig infusion related adverse events	Efficacy: IgG levels were higher following IgRT (474 mg/dL vs 380 mg/dL) Annual rate of serious bacterial infections was 0.46 per patient year before IgRT and 0.10 per patient year following IgRT Annual rate of infections was 2.79 versus 2.29 before and after IgRT Safety: 10% of SCIG patients had infusion-site reactions

[Shankar et al, 2013] Single centre, US Retrospective analysis of electronic medical records Vivaglobin and IgPro20 One loading dose of IVIG (5% Gammaguard liquid at 400 mg/kg), then Vivaglobin or IgPro20 100 mg/kg weekly	Study duration: 6 to 12 months *N* = 10 Age of participants: mean age 59.9 years Sex: 60% male	Inclusion: single or bilateral lung transplant recipients who had immunoglobulin levels assessed and were started on subq IgG replacement therapy Exclusion: Patients with known pre-transplant immune-deficiencies	Efficacy: Immunoglobulin levels, allograft function Safety: Tolerability, occurrence and treatment of infection	Efficacy: All 10 patients demonstrated increase in IgG levels at 3 months that was sustained at 6 to 12 months Safety: 7 patients (70%) had no complications; 3 patients (30%) experienced local infusion site reactions (swelling, erythema, soreness) that resolved spontaneously within 24 h. Two patients were on Vivaglobin therapy and one patient on IgPro20 at time of local reaction. No patients experienced worsening renal function, respiratory distress, cardiovascular compromise, or required epinephrine treatment
IVIG and SCIG				
[Spadaro et al, 2016] Single centre, Italy Non- randomized cross-over (IVIG vs SCIG) IgVena, Kiovig, Flebogamma (10%) Switched to IgPro20 (20%) or Subcuvia (conc. not specified) after 6 months Mean 400 mg/kg/month IVIG Mean 100 mg/kg/week SCIG	Study duration: 8 months N = 14 Age of participants: 61 years Gender: 50% male	Inclusion: Treated for at least 6 months with rituximab-including chemotherapy, hypogammaglobulinemia (IgG < 4g/L) for at least 12 months after rituximab treatment Exclusion: Protein-losing diseases	Efficacy: Serum IgG concentration Incidence of infections Safety: Not stated	Efficacy: Mean serum IgG level after discontinuation of rituximab was 251.36 ± 105.65 mg/dL (range: 60 to 400 mg/dL). Mean serum levels of IgG were higher during replacement therapy than at the end of rituximab treatment ($p < 0.001$) During IVIG and SCIG replacement therapy mean number of infectious events was 3.0 ± 1.4 and 2.4 ± 1.4 respectively compared with a mean of 11.1 infections prior to therapy
[Reiser et al, 2017] Multicentre, Germany Non-interventional prospective study Any marketed SCIG or IVIG SCIG average: 343 mg/kg every 4 weeks (p=0.003) Average dose 205 mg/kg every 4 weeks IVIG average: 199 mg/kg every 4 weeks	Study duration: Average follow-up 20.5 months N = 307 Age of participants: 63.7 years Gender: 52% males	Inclusion: Any age, receive IgRT as long-term maintenance or new therapy. Patients with SID were included (CLL, NHL, MM or HIV owing to infections or tumours related to HIV) Exclusion: Not stated	Efficacy: Infection rate and QoL Safety: Side effects	Efficacy: Annual rate for serious infections was 0.122 and 0.036 for SBIs during IgRT. In newly treated IgRT patients, 82% had an infection prior to IgRT vs 65% following IgRT QoL assessed as moderate or good Safety: 15 AEs were reported on IVIG; 4 SAEs leading to hospitalisation No AEs reported on SCIG

[Benbrahim et al, 2019] Observational, multicentre, France Non-interventional, observational, multicentre, prospective longitudinal study Octagam (10%) and Gammanorm (SCIG) 50 patients initiated IVIG; 110 initiated SCIG. Mean monthly dose of 387 ± 78 mg/kg for IVIG versus mean weekly dose of 97 ± 45 mg/kg for SCIG [resulting in a mean monthly dose of 388 mg/kg]	Study duration: mean follow-up 8.7 months ± 4.0 months N = 160 (MM: 54; CLL: 54; aggressive NHL: 19; indolent NHL: 29; Hodgkins disease: 4) Age of participants: Mean 67.3 years Gender: 61.9% male	Inclusion: Adult patients newly prescribed IgRT for HM-associated SID Exclusion: Not stated	Efficacy: Number and type of infections, Serum Ig levels Safety: AEs	Efficacy: Sepsis decreased after IgRT from 2.43 to 1.90 (p = 0.001); Infections needs IV antibiotics decreased from 0.45 to 0.27/year Serum Ig increased by 3.4 ± 2.4 g/L Safety: No SAEs were reported during the study; 6 patients reported AEs (pneumonia, itching, blood pressure increase, rash and cold sensation) 17 patients died

Summary of main studies

Trials performed with Hizentra (IgPro 20) in SID encompassed:

- Vacca et al 2018, a prospective, controlled, randomised 18-month study in 46 multiple myeloma (MM) patients (24 on IgPro20 and 22 controls) with IgG <500 mg/dL who received a monthly total dose of 0.4 to 0.8 g SCIg/Kg. Various patient characteristics were well-balanced between the 2 arms. Anti-myeloma therapy consisted of Bortezomib, IMIDs or chemotherapy, Approx 28% had received previous autologous stem cell transplantation (ASCT). None of the enrolled patients received ASCT during the study. No patient received antibiotic prophylaxis.

The primary endpoint was the annual rate of severe infections (**Table 2**). Median IgG trough levels ranged from 8.3 to 9.5 g/L in the verum group and from 2.4 and 5.2 g/L in the control arm group. A significantly lower number of infections ($p < 0.001$) were observed in the SCIg group. There were 16 major infections episodes in the SCIG group and 190 in the control group. The differences between the 2 arms were also significant for total number of infections, respiratory infections, days in hospital/y and days under antibiotic treatment/y.

Table 2. Total number of infectious episodes during the study

Total number of infectious episodes during the study.

	Patients	
	Arm-A: SCIg	Arm-B: controls
Major infections		
Sepsis	–	24
Bacterial pneumonia	–	18
Bronchitis with sepsis	–	43
Pharyngo-tracheitis with sepsis	2	24
Acute sinusitis	–	5
Erysipelas	–	12
Urinary infection with sepsis	1	32
Fever of unknown origin	13	32
Minor infections		
Tracheobronchitis	32	64
Bacterial skin infection	11	16
Bacterial stomatitis	6	12
Lower urinary tract infection	19	36
Thoracic herpes zoster	1	15

- Campagno et al, 2014, single centre, retrospective study in 61 patients with rituximab-related SID. Mean duration of SCIG was 19 months; 35 pts on Subcuvia, 26 on Vivaglobin who then switched to Hizentra. Mean dose SCIG was 75 mg/week. 31/61 had been previously treated with IVIG (wash-out/wash-in of 15-22 days). Therapy was started at IgG < 600 mg/dl and concurrent serious non-neutropenic infections (> 2 episodes in 12 months). Serum trough levels were higher with SCIG compared to IVIG, which is to be expected. SCIG showed better general tolerability and safety, but more infusion site reactions. Serious infections (pneumonia, meningitis, endocarditis, sepsis) occurred in 24/61 patients pre-IG treatment (0.46 episodes/pt/y) and dropped 4-fold in 12/33 SBIs under IVIG (0.10 episodes/pt/y) and 11/61 SBIs under SCIG (0.11 episodes/pt/y).

Although efficacy and safety are shown for SCIG, it remains unclear from the Campagno study when the patients were switched from Vivaglobin to IgPro20 and how much of the latter they received. Thus, although the data are consistent and supportive, it is difficult to draw clear conclusions specifically for IgPro20. The MAH was requested to ascertain how many patients received which amount of Hizentra. In response, the MAH has quoted the information from the Compagno article on the 26 patients receiving Hizentra. Further details are not provided; the MAH could have contacted the author.

However, as mentioned above, the efficacy and safety data on the 61 patients treated with SCIG at a mean dose of 75 mg/kg/week (Subcuvia/Vivaglobin/Hizentra) are consistent with other SCIGs. Both IVIG and SCIG reduced yearly SBIs four-fold compared to pre-Ig treatment. The response was considered acceptable.

- Shankar et al 2013, retrospective analysis of the efficacy and tolerability of subcutaneous immunoglobulin replacement on 10 lung-transplant recipients. Hypogammaglobulinemia as defined by IgG below 500 mg/dl, but patients were also included if their level was below 750 mg/dl and they had recurrent infections (e.g., 2 episodes of pneumonia per year). 4 patients received Hizentra and 6 received Vivaglobin, but all eventually transitioned to Hizentra when production of Vivaglobin was discontinued. All 10 patients demonstrated an increase in IG levels at three months that was sustained at 6–12 months with SCIG replacement therapy, with the majority (70%) tolerating infusion without complications. 3 infusion site reactions were seen (2 with Vivaglobulin and 1 with Hizentra)

The data from the Shankar study are consistent with the other data provided, showing increases of IgG levels under SCIG therapy in lung-transplant recipients. As it was difficult to draw distinct conclusions for Hizentra due to the overlap of Vivaglobin. The MAH was requested to ascertain how many patients

received which amount of Hizentra. In response, the MAH provided information from the Shankar article on the 4 patients receiving Hizentra. The MAH could have contacted the author. Nevertheless, the study suggests that SCIG therapy is well tolerated and leads to reliable increases in IgG levels. The response was considered acceptable by the CHMP.

- Spadaro et al 2016, a non-randomised cross-over study in 14 patients with a B-cell lymphoproliferative disease (12 with NHL and 2 with CLL) who had been treated for at least 6 months with a rituximab-including chemo-immunotherapy regimen. In all patients hypogammaglobulinemia (IgG 400 mg/dl) was detectable for at least 12 months after discontinuation of rituximab. Patients were treated initially with IVIG at a mean dose of 400 (± 15.7) mg/kg/month, with an interval between each infusion of 3 weeks. Seven patients received IgVena (Kedrion), 4 patients used Kiovig (Baxter), and 3 patients Flebogamma (Grifols). After six months of IVIG therapy, all patients were switched to SCIG therapy at a mean dose of 100 (± 4.4) mg/kg/week, with an interval between each infusion of one week (10 patients received Hizentra and 4 patients Subcuvia). Mean serum levels increased under IVIG to within normal ranges and increased again under SCIG. Infections (both higher and lower respiratory tract infections and gastrointestinal infections) were considerably reduced under replacement therapy. Previously, (i.e. before replacement therapy mean infections were 11.1±3 – this was reduced to 3±1.4 under replacement therapy.

These data support the above findings, showing increases of IgG levels under IVIG and further increases under SCIG. The definition of infections is slightly different in this study (i.e., not delineating SBIs) – however, the >3-fold reduction of infections under both administration routes (IVIG and SCIG; 10 patients on Hizentra) is clear.

Trials with SCIG /IVIG either without Hizentra, or where the brand is not mentioned:

- Dimou et al 2018; in a retrospective single centre study, 33 SID patients with haematological malignancies were treated with HyQvia, 13/33 were already on IVIG before switching. All patients had ≥2 severe bacterial infections in the 12 months prior to treatment. The treatment goal for all patients was IgG trough levels around 600 mg/dl. The dose of fSCIg (10% IgG) was 0.4-0.8 mg/kg/month with dose intervals between 3-4 week. 29 patients remained on HyQvia, 3 patients died due to the underlying illness and 1 switched to IVIG due to a rash. 6 patients had infections (all had IgG levels < 600 mg/dL), 5 were then put on shorter intervals and no new infections occurred. Data from 6 months after HyQvia administration shows trough levels in 17 patients above 600 mg/dL. The ADRs were generally mild and reflect those described in the product's SmPC.

Data from this small, retrospective study in patients with haematological malignancies treated with HyQvia are generally sparse esp. for 12 and 24 months, but they remain supportive for replacement therapy in SID patients.

- Reiser et al 2017; the SIGNS study was a prospective, long-term (FU 3y/pt) non-interventional study (NIS) (ClinicalTrials.gov: NCT01287689). Forty-eight centres throughout Germany enrolled 307 SID patients (CLL, MM, indolent lymphoma, and other malignancies such as non-Hodgkin lymphoma or HIV). Particular focus of the study was the annual SBI rate. 31% were newly treated with IGs and 69% were on maintenance therapy. Significant differences in doses were seen between patients on IVIG (199 mg/kg per 4 weeks) compared those on SCIG (343 mg/kg per 4 weeks, p=0.003); however only 20 patients received SCIG (6.5%). Median plasma trough levels did not differ remarkably in the course between patients with recommended dosing and those with lower than recommended doses (threshold at 200 mg/kg every 4 weeks, p=0.274).

Before treatment with IVIG/SCIG the SBI/pt/y was 0.250, after treatment this dropped 7-fold to 0.036.

15 reports on adverse events were received (see Safety Section)

This interesting NIS provides the largest current dataset of patients with SID treated with IG under real-life conditions and supports the data above, albeit in a small number of patients receiving SCIG (n=20/307). The IVIG dosing that was generally at the lower end of recommendations (mean: 205 mg/kg per month) and led to median trough levels of about 6 g/l, was nevertheless efficacious in decreasing infection rates. IgRT was interrupted in every fourth patient due to "drug holidays" in the summer months when the risk of infections spontaneously decreases.

- Benbrahim et al 2019; this was a non-interventional, longitudinal, prospective French study (21 sites) in 160 patients starting IgRT (octagam (IVIG) and gammanorm (SCIG)) for hematological malignancies associated with SID. It was part of a larger study (Benbrahim et al 2018 in 238 patients), whereby this subgroup analysis for patients receiving octagam or gammanorm had been prospectively planned. The patients were followed-up for 8.7 ± 4.0 months. 17 patients died (5 of sepsis). lgRT was initiated with IVIg in 50 patients (31.3%) and with SCIg in 110 (68.8%) patients; with a total of 398 IVIg and 3421 SCIg infusions. Mean monthly doses were the same for both routes.

Treatment was discontinued in 9% of patients, stopped for futility in 31% (i.e the patient was no longer at risk of infection), temporally interrupted in 8%, suspended during summertime in 14% (drug holiday) and pursued without interruption in 38% of patients. In addition, IgRT was stopped by 15 patients (9.4%) for personal convenience (N = 9), lack of efficacy (N = 3), tolerance concern (N = I), organizational problem (N = 1).

Compared to baseline, lgRT increased serum IgG levels from 4.7 ± 3.4 g/L to 7.7 ± 2.8 g/L. The proportion of patients with serum lgG levels <5 g/L decreased from 69.2% at baseline to 15.9% at last visit whatever the route of administration. 37% had ≥1 infection leading to hospitalisation in the 12 months prior to study entry. The annual incidence of infections dropped from 2.43 to 1.90. Infections leading to hospitalisation decreased from 0.58/pt/y to 0.31/pt/y (p= 0.04) this decrease was mainly seen in the relapsed or refractory patients. IgRT was well tolerated. No serious adverse events were recorded during the study, (see Safety Section).

In keeping with the other data, lgRT increased serum IgG levels (by 3.4±2.4 g/L) and decreased frequency and severity of infections compared to baseline. Overall, the products octagam or gammanorm were well-tolerated. Published SCIG doses are as shown in **Table 3**.

Table 3. Published SCIG doses in SID

Indication	SCIG dose	Reference
CLL, NHL	Subcuvia, Vivaglobin or IgPro20 75 mg/kg/week	[Compagno et al, 2014b]
Hematologic malignancies	SCIG 350-500 mg/kg/month	[Benbrahim et al, 2019; Na et al, 2019]
MM	IgPro20 400-800 mg/kg/month	[Vacca et al, 2018]
Lung transplantation	Vivaglobin or IgPro20 100 mg/kg/week	[Shankar et al, 2013]
Primary intestinal lymphangiectasia	10 g/week	[Aytekin et al, 2019]
Hematologic malignancies	343 mg/kg/month	[Reiser et al, 2017]
Protein-losing enteropathy after Fontan surgery	IgPro20 90 -120 mg/kg/week	[Kagiyama et al, 2018]
PID and SID	IgPro10/20 150 mg/kg/week	[Shillitoe et al, 2018]

CLL = Chronic lymphocytic leukemia, MM = multiple myeloma, NHL = non-Hodgkin lymphoma, PID = Primary immunodeficiency, SCIG = Subcutaneous immunoglobulin, SID = Secondary immunodeficiency

Analysis of IgG doses used for treatment of 6000+ patients with PID and SID (of these, 845 were SID patients) in the United Kingdom [Shillitoe et al, 2018] demonstrates that mean doses of IgG products in 37 clinical centres were around 600 mg/kg/month, equivalent to 150 mg/kg/week.

The doses provided from the literature mainly lie within the range recommended for SCIG for PIDs, i.e., a cumulative monthly dose of the order of 0.4 to 0.8 g/kg. However, lower doses may be equally efficacious in SID e.g., Compagno also demonstrated efficacy at SCIG doses of 75 mg/kg/week (300/kg/month). As mentioned in the SCIG coreSmPC for PID patients, the dose regimen should achieve a trough level of IgG of at least 5- 6 g/L. This in turn will depend on tailoring to the patients' needs and should be assessed in conjunction with the incidence of infection. A similar approach should be taken with SID patients.

Interestingly, 2 studies mentioned "drug holidays" when IgRT was interrupted in the summer months due to the lower risk of infections. This concept is not specifically mentioned in the coreSmPC or product specific SmPCs but may be considered as part of the approach of individual tailoring of doses and dosing intervals.

Practice Guidelines

The MAH has also given consideration to international practice guidelines. Additional details are presented in **Table 3.**

Table 3. Guidelines for SID Therapy

Title (Reference)	Authority	Year	Outcome/Conclusions
[Anderson D, et al, 2007]	Canadian Blood Services/ National Advisory Committee on Blood and Blood Products of Canada panel	2007	• These guidelines from a panel of Canadian experts were gathered by the National Advisory Committee on Blood and Blood Products of Canada and Canadian Blood Services • IVIG is recommended for infection prophylaxis in adults with malignant hematologic disorders associated with hypogammaglobulinemia (no definition specified) and either a recent life-threatening infection thought to be caused by low IgG, or recurrent clinically significant infections thought to be caused by low IgG (no definition of hypogammaglobulinemia / low IgG provided) • Consider other contributing factors for infection in determining the likely role of hypogammaglobulinemia • 0.4 g/kg every 3 weeks with re-evaluation every 4 to 6 months recommended
[UK Department of Health. Clinical guidelines for immunoglobulin use, 2011]	UK Department of Health	2011	• These guidelines from UK Department of Health summarise Ig use • Recommend IgRT (0.4 g/kg every 4 weeks adjusted for individual IgG trough levels) if the cause of hypogammaglobulinemia cannot be reversed or in patients with hypogammaglobulinemia associated with CLL, MM or other B-cell malignancy, and - Recurrent or severe bacterial infections despite oral antibiotic use for 3 months - IgG levels < 5 g/L - Failed antibody response to polysaccharide vaccine • IgRT use in secondary immunodeficiency was moved from grey (weak evidence) to blue (sufficient evidence) recommendation (grade C recommendation, level III evidence)
[Eichhorst et al, 2015]	European Society for Medical Oncology (ESMO)	2015	• This publication summarises ESMO guidelines • The use of prophylactic systemic immunoglobulin does not have an impact on overall survival in CLL • IgRT only recommended in patients with severe hypogammaglobulinemia and repeated infections (grade A recommendation, level III evidence) (no definition of severe hypogammaglobulinemia provided) • Antibiotic and antiviral prophylaxis should be used in patients with recurrent infections and / or very high risk of developing infections

[Moreau et al, 2017]	ESMO	2017	• This publication summarises ESMO guidelines • Infectious episodes require therapy with antibiotics • Prophylaxis of infections may be beneficial within first 2 to 3 months of therapy, especially in patients at high risk of developing infections • IVIG in patients with MM is not recommended as prophylaxis for infections by ESMO
[Perez et al, 2017]	AAAAI working group	2017	• These guidelines were developed by a working group for AAAAI • IgRT should be considered in: - Patients with CLL or MM, and lymphoma treatment with B-cell depleting therapies - Patients with hypogammaglobulinemia and recurrent bacterial infections and sub-protective antibody levels after immunization against diphtheria, tetanus or pneumococcal infection (no definition of hypogammaglobulinemia provided) • Prophylactic use of IVIG should be considered in elderly patients with recurrent, severe, or difficult to treat infections if paired with deficient antibody function
[Alberta Government. Criteria for the clinical use of immune globulin, 2018]	Alberta Government	2018	• These guidelines summarise recommendations for Australia, Canada and the UK • Different countries have varying criteria for recommending IgRT, from history of recurrent or severe infections, to IgG levels < 4 g/L and the proven failure of antibiotics • Suggested doses varying between 0.3 to 0.5 g/kg every 3 to 4 weeks - Subcutaneous IgG can be considered as an alternative to IVIG, suggested dose 0.1 g/kg weekly
[Mikulska M, et al, 2018]	ESCMID Study group for infections in compromised hosts	2018	• These guidelines summarise recommendations by ESCMID • CD19-targeted agents may cause hypogammaglobulinemia and neutropenia • Infection is the most common non-haematological adverse event associated with CD19 agents • Clinicians should be aware of the increased risk of hypogammaglobulinemia, neutropenia, and the associated infectious complications • In cases of severe hypogammaglobulinemia, particularly in case of recurrent infections (no definition of severe hypogammaglobulinemia provided), IgRT according to local guidelines could be considered

AAAAI = American Academy of Allergy, Asthma & Immunology, CLL = Chronic lymphocytic leukemia, ESCMID = European Society of Clinical Microbiology and Infectious Diseases, ESMO = European Society for Medical Oncology (ESMO), IgG = immunoglobulin G, IgRT = immunoglobulin replacement therapy, IVIG = intravenous immunoglobulin, MM = multiple myeloma, SID = Secondary immunodeficiency, UK = United Kingdom

To a great extend these international Practice Guidelines recommend that SID patients with severe hypogammaglobulinemia and repeated infections receive doses of ~ 0.3 -0.5 g/kg every 3-4 weeks. A number of GLs do not recommend prophylactic immunoglobulin use.

2.4.2. Discussion on clinical efficacy

Background

For the initial Marketing Authorisation, the Applicant provided adequate PK, efficacy and safety data for Hizentra (IgPro20) in PID patients in both European and US studies. Under the stipulations of the SCIG GL (EMA/CHMP/BPWP/410415/2011 rev 1) the indication hypogammaglobulinemia due to the SIDs CLL, MM and HSCT were granted without further studies. The MAH now seeks to extend the latter indications to cover a wider group of SID syndromes as delineated in the IVIG coreSmPC.

SID studies with Hizentra

The MAH submitted a literature review of studies both with Hizentra in SID patients and as supportive evidence studies with other IVIG/SCIG products. As mentioned above SCIGs can be viewed as a class of biologics that have shown similar efficacy in the PID setting and for CLL and MM. Thus, it is considered acceptable to base this application on a literature review.

A well-designed trial performed by Vacca et al (2018) and independently of CSL Behring, was a prospective, controlled, randomised 18-month study in 46 MM patients (24 on IgPro20 and 22 controls) with hypogammaglobulinemia (IgG <500 mg/dL) who received doses of 0.4 to 0.8 g SCIg/kg/month. The primary endpoint was the annual rate of severe infections. Median IgG trough levels ranged from 8.3 to 9.5 g/L in the verum group and from 2.4 and 5.2 g/L in the control arm group. A significantly lower number of infections ($p < 0.001$) were observed in the SCIg group. There were 16 major infections episodes in the SCIG group and 190 in the control group. The results unequivocally show that Hizentra administration to MM patients results in a reduced rate of infections, a shorter length of hospitalization and a lower number of days of antibiotic therapy. This prospective, controlled study clearly supports the efficacy of IgPro20 in MM patients with hypogammaglobulinemia. Side-effects were in the range of those expected with SCIGs.

The other studies with Hizentra performed by Campagno, Shankar and Spadaro support these efficacy data. In addition to the indication MM of the Vacca study, these 3 studies included 61 patients with rituximab-related SID, 10 lung-transplant recipients and 14 patients with a B-cell lymphoproliferative disease and rituximab-related SID, respectively. Definitions of hypogammaglobulinemia varied slightly among the 3 studies (600 mg/dL, 500 mg/dL, 400 mg/dL respectively).

Other supportive studies

Further studies either without Hizentra, or where the brand is not mentioned encompass those by Dimou, Reiser, and Benbrahim. The Dimou study was a retrospective study in 33 patients with haematological malignancies treated with HyQvia and aimed at providing IgG trough levels above 600 mg/dL (achieved in 17 pts at 6 months). However, the data are generally sparse, but could be considered supportive for replacement therapy in SID patients. The Reiser trial was a NIS in 307 patients with various underlying SID conditions; 20 patients thereof received SCIG, the other patients received IVIG. Median trough levels of about 6 g/l were reached, despite slightly lower dosing regimens (IVIG: 205 mg/kg per month); SBIs/pt/y dropped 7-fold after treatment to 0.036. The Benbrahim study was a NIS, prospective French trial in 160 patients receiving octagam (IVIG) and gammanorm (SCIG)) for hematological malignancies associated with SID. lgRT increased serum IgG levels (from 4.7 ± 3.4 g/L to 7.7 ± 2.8 g/L.) and decreased frequency and severity of infections compared to baseline.

Dosing

The doses provided from the literature studies mainly lie within the range recommended for SCIG for replacement therapy, i.e., a cumulative monthly dose of the order of 0.4 to 0.8 g/kg. Some of the studies submitted, indicated that lower doses may be feasible. In general, an IgG trough level of above 600 mg/dL is considered protective for most serious infections for the majority of PID/SID patients. Tailoring of doses is deemed essential and should always be performed in conjunction with the infection rate of a given individual. Hence in studies in replacement therapy, regardless of the pathogenesis of the hypogammaglobulinemia (PID or SID), one of the aims is to achieve a trough level above 600 mg/dL.

International Practice Guidelines

International Practice Guidelines support the use of IgRT for SID patients, at doses of approx. 0.4 g/kg every 3-4 weeks to be adjusted for individual IgG trough levels.

2.4.3. Conclusions on the clinical efficacy

The total data set submitted by the MAH is considered sufficient to support the efficacy of Hizentra in SID patients.

2.5. Clinical safety

Introduction

In the initial Marketing Authorisation, the Applicant provided adequate PK, efficacy and safety data for Hizentra (IgPro20) in PID patients in both European and US studies that led to the authorisation in 4/2011.

Literature review (as used for efficacy above)

Vacca et al showed in 46 multiple myeloma (MM) patients (24 on IgPro20 and 22 controls) that ADRs were predominantly mild, and in only 3 patients did their severity require the discontinuation of the SCIg infusion: 2 of them experienced pain and inflammatory reaction at the site of injection, and one showed an extensive allergic skin reaction after the second administration that resolved following steroid and antihistamine therapy.

In 61 patients (33 previously on IVIG) treated for SID secondary to B-cell lympoproloferative disorders Campagno et al showed that SCIG had better general tolerability and safety than IVIG, but more infusion site reactions. Only 2 patients (2/61) decided to return to the IVIG route of administration due to poor local tolerance and only 1/61 required pre-medication.

In the study by Shankar et al the majority (7/10 - 70%) tolerating infusion without complications. 3 infusion site reactions were seen (2 with Vivaglobulin and 1 with Hizentra)

In the Reiser study with various IVIGs and SCIGs there were 15 reports on adverse events (11 non-serious and 4 serious leading to hospitalisation) were obtained on the various lgG agents (all intravenous, none on subcutaneous preparations). Events were specified as allergic reactions (2 patients), chills (5), back pain (1), thoracic pain (1), (severe) nausea (3), pleuritis (1), dizziness (1), and mild proctitis (1).

In the octagam (IVIG) and gammanorm (SCIG) study by Benbrahim no serious adverse events were recorded during the study. Only 6 patients (3.7%) reported adverse events: pneumonia (IVIg), itching/ swelling/redness (2 patients, SCIg), blood pressure increase (IVIg), and rash (SCIg), cold sensation/asthenia (SCIG).

Post marketing experience

During the reporting period of the latest PSUSA EMEA/H/C/PSUSA/00001633/202005 (01/06/2017 - 31/05/2020), safety related changes were made to the RSI. These included:

- Updates due to the completed clinical studies PATH (IgPro20_3003) and
- PATH Extension (IgPro20_3004) in CIDP patients.
- Updates due to the completed Phase IV safety and tolerability study on higher
- Infusion parameters (IgPro20_4004) in PID patients.
- Updates due to the completed Phase IV study on biweekly dosing regimen
- (IgPro20_4005) in PID patients.

Cumulatively 309 patients have been enrolled into the Hizentra clinical program, 222 subjects with PID (primary immunodeficiency), 82 subjects with CIDP (chronic inflammatory demyelinating polyneuropathy), 3 subjects with SSc (systemic sclerosis) and 2 subjects with DM (Dermatomyositis).

For Hizentra reporting rates of well-known adverse reactions, based on safety data from the current PSUSA interval stay in the expected range. For serious adverse reactions "hypersensitivity", "thromboembolic events", "aseptic meningitis", "haemolysis" and "renal failure" no increases in the reporting rate were documented.

Localized infusion site reactions and deep skin ulcerations (UL-ISR) represent a specific problem with the subcutaneous administration of Hizentra. A total of 25 suspected cases of UL-ISR (including 10 of infusion site necrosis) were identified during this reporting interval. These cases of UL-ISR occurred in 6 paediatric patients, 10 adult patients, and 4 elderly patients (5 unknown). At the time of reporting, the outcomes were as follows: resolved (3), resolving (4), resolved with sequelae (3), not resolved (5), unknown/not reported (10). Although underlying diseases and improper administration technique may contribute to these complications, it remains a serious adverse reaction, especially in paediatric patients.

Safety in SID

CSL Behring performed a review to determine the safety profile of IgPro20 (Hizentra) when used in patients with SID, as compared to the known safety profile in patients with PID. All post-marketing and clinical trial cases received until 31 December 2020 reporting indications consistent with use in SID, per the Standardised MedDRA Query (SMQ) Haematological malignant tumours and / or the High-Level Term Acquired Immunodeficiency Syndromes; as well as all cases reporting indications consistent with use in PID, per the High-Level Term Primary Immunodeficiency Syndromes, were retrieved from the CSLB safety database.

Most frequently reported AEs (SID vs PID)

A total of 1906 SID cases (with 5066 AEs) and 8697 PID cases (with 23724 AEs) were identified in patients treated with Hizentra. The vast majority of the SID cases originated from Canada (1537/1906,

80.6%), where Hizentra is already indicated for the treatment of patients with PID and SID who require immunoglobulin replacement therapy. Almost all of these Canadian cases (1525/1537, 99.2%) were received from the local Patient Support Program.

An analysis of the most frequently reported adverse events (≥ 1% in either PID or SID) from all cases, compared by PID or SID indication, is presented in **Table 4**. The events for the SID indication were consistent with the most frequently reported events for the PID indication.

Table 4 Most frequently reported AEs by indication (any AE ≥ 1%)

Preferred term	SID indication (n = 5066) AE %	PID indication (n = 23724) AE %
Infusion site erythema	4.22%	2.66%
Injection site erythema	3.97%	1.14%
Fatigue	3.83%	3.42%
Headache	2.74%	4.76%
Infusion site swelling	2.72%	2.24%
Infusion site pain	2.03%	2.26%
Injection site swelling	2.03%	0.67%
Nasopharyngitis	1.88%	0.94%
Pneumonia	1.78%	1.35%
No adverse event	1.70%	0.71%
Injection site pain	1.64%	0.78%
Infusion site bruising	1.28%	0.60%
Pruritus	1.22%	1.57%
Malaise	1.18%	0.93%
Nausea	1.11%	2.28%
Injection site mass	1.05%	0.15%
Diarrhoea	0.99%	1.06%
Pyrexia	0.93%	1.58%
Rash	0.85%	1.39%
Sinusitis	0.81%	3.97%
Pain	0.79%	1.56%
Infusion site pruritus	0.65%	1.24%
Bronchitis	0.32%	1.40%

AE = adverse event, n = total number of events, PT = preferred term, PID = primary immunodeficiency, SID = secondary immunodeficiency

[a] Reported as a PT for special situations such as medication errors and drug exposure during pregnancy

The most commonly reported, relevant primary indication from this 1906 SID case subset were the PTs SID (1742 cases, 91.4%), CLL (33 cases), and Plasma cell myeloma (19 cases - the LLT Multiple myeloma feeds into the PT Plasma cell myeloma). However, based also on the reported secondary indication, concomitant diseases and comedication, a declared or reasonably suspected cause for SID could be identified in 1446 cases (75.9%, with 3766 AEs; thereof 1770 AEs in approved SID indications and 1996 in "off-label" SID indications). About half of the cases with identifiable cause of SID (666 of 1446 cases, with 1770 AEs) included the already approved indications in EU of Chronic lymphocytic leukaemia (430 cases, 22.6%), Plasma cell myeloma (210 cases, 11.0%), and

Haematopoietic stem cell transplantation (26 cases, 1.4%). The second half of cases with identified causes of SID (780 of 1446 cases, with 1996 AEs) consisted of other haematological malignancies (372 cases, 19.5%), iatrogenic causes (radio/chemotherapy or immunosuppressant treatment, 194 cases, 10.2%), Non-Hodgkin lymphoma (87 cases, 4.6%), other neoplasms (71 cases, 3.7%), solid organ transplant (35 cases, 1.8%), and other diseases (21 cases, 1.1%). Thus, this dataset contains safety data of the variety of SID conditions including several diagnoses not currently approved for IgPro20 in EU.

Table 5. Reasonably suspected cause for SID in **1446 cases** (with 3766 AEs)

	SID indication already authorised for Hizentra (n= cases)	SID indication not currently authorised for Hizentra (n= cases)
CLL	430 (22.6%)	-
Myeloma	210 (11%)	-
HSCT	26 (1.4%)	-
Other haematological malignancies		372 (19.5%),
Iatrogenic causes (radio/chemotherapy or immunosuppressant treatment)	-	194 (10.2%)
Non-Hodgkin lymphoma	-	87 (4.6%),
Other neoplasms	-	71 (3.7%),
Solid organ transplant,	-	35 (1.8%)
Other diseases	-	21 (1.1%)
Total	**666 (46%)**	**780 (54%)**

The MAH provided a comparison of the most frequently reported AEs in cases with SID indications in line with the EU approved label (ie, CLL, Plasma cell myeloma (Lowest Level Term Multiple myeloma feeds into it) and Haematopoietic stem cell transplantation) vs other non-EU approved SID indications (> 1% in either of them) as shown in **Table 6.**

Table 6. Most frequently reported AE by EU approved SID indication (any event ≥ 1%)

Preferred term	EU approved SID indications (n = 1770) AE %	Non-EU approved SID indications (n = 1996) AE %
Infusion site erythema	3.56%	4.61%
Injection site erythema	3.45%	4.21%
Fatigue	3.39%	4.06%
Headache	2.99%	2.76%
Infusion site swelling	2.94%	2.61%
Infusion site pain	2.32%	1.70%
Nasopharyngitis	1.86%	2.10%
Injection site pain	1.86%	1.60%
Infusion site bruising	1.64%	0.90%
Injection site swelling	1.58%	2.30%
Pneumonia	1.53%	2.10%
Death	1.47%	0.90%
No adverse event	1.41%	1.55%
Diarrhoea	1.24%	0.75%
Infusion site mass	1.24%	0.65%
Pyrexia	1.13%	0.80%
Malaise	1.07%	1.15%
Pruritus	1.02%	1.45%
Dizziness	1.02%	0.35%
Nausea	0.85%	1.30%
Injection site mass	0.85%	1.05%
Erythema	0.73%	1.05%
Sinusitis	0.68%	1.00%

AE = adverse event, EU =European Union, SID = secondary immunodeficiency

Overall, the most frequently reported AEs for the SID indication (either approved in EU or not) are consistent with the known safety profile for Hizentra specified in the Reference Safety Information (Company Core Data Sheet, version 6.0, dated 12 June 2019) and the EU SmPC; or are expected events in the population of use which are likely attributable to the patient's underlying illness. This includes:

- Local reactions (infusion/injection site erythema, infusion site pain, infusion/injection site swelling, infusion site pruritus, infusion site bruising, infusion site mass)
- Hypersensitivity reactions (pruritus, rash)
- General or nonspecific reactions (headache, fatigue, nausea, pyrexia, pain, diarrhoea, vomiting, malaise, chills)

- Events consistent with patient's underlying immunodeficiency conditions (sinusitis, pneumonia, bronchitis, upper respiratory tract infection, nasopharyngitis).

Among the total of 5066 AEs, the case series for SID includes also coded PTs which represent outcomes (Death), efficacy (Drug ineffective), no events (No AE) or are not specific (Ill-defined disorder):

- 50 SID cases reported an event of Death. All were considered either unassessable due to insufficient information, or unlikely related/not related, due to more plausible alternative explanations such as advanced age or underlying conditions such as CLL or MM. The vast majority of source for these cases were Patient Support Programs (45/50), of which 30 received from a consumer reporter type. There is no new significant safety information identified from these events.
- 50 SID cases reported an event of drug ineffective. In general, a lack of effect is considered expected as 100% success rate cannot be reasonably assumed in every patient. Most were considered either unassessable due to insufficient information, or not related, due to more plausible alternative explanations such as complex underlying conditions. The vast majority of source for these cases were Patient Support Programs (44/50), of which 37 received from a consumer reporter type. There is no new significant safety information identified from these events.
- In 84 SID cases the PT No Adverse Event was also coded (n = 86); the majority of these reports were due to therapy or posology compliance issues (therapy cessation or interruption, dose omission), medication errors, or use in unapproved indication. There is no new significant safety information identified from these events.
- 39 SID cases reported an event of Ill-defined disorder (n = 40), the majority of which were nonspecific reports of the patient being "unwell" or "sick". There is no new significant safety information identified from these events.

Overall, there were no new safety concerns for the SID population identified from review of these cases in comparison to those of the PID population treated with Hizentra. Furthermore, the safety profile observed for Hizentra in SID does not significantly differ between the EU approved indication and the wide concept of SID, and it is largely consistent with the known safety profile of Hizentra, as described in the current RSI, EU SmPC, and Risk Management Plan.

Moreover, CSL Behring performs regular reviews of all safety data during routine signal detection, risk management planning and aggregate reporting activities. No differences in the safety profile between indications or any overall new safety concerns in the SID indication have been identified during these activities.

2.5.1. Discussion on clinical safety

Although sparse in nature, the literature review shows that the side effects with SCIG therapy in SID reflect those depicted in the SmPC of Hizentra. Mostly the ADRs concerned infusion site reactions which were mainly mild, although some more severe skin reactions did occur

To further determine the safety profile of Hizentra when used in patients with SID, (as compared to the known safety profile in patients with PID), all post-marketing and clinical trial cases received until 31 December 2020 reporting indications consistent with use in SID were evaluated by the MAH.

A total of 1906 SID cases (with 5066 AEs) and 8697 PID cases (with 23724 AEs) were identified in patients treated with Hizentra. The majority of the SID cases originated from Canada (1537/1906, 80.6%), where Hizentra is already indicated for the treatment of patients with PID and SID who require immunoglobulin replacement therapy. A declared or reasonably suspected cause for SID could be identified in 1446 cases (75.9%, with 3766 AEs; thereof 1770 AEs in approved SID indications and 1996 in "off-label" SID indications).

The comparison of this post-marketing data show that the safety profile of Hizentra in PID and SID patients is similar and that this also holds true within the SID indications (approved CLL, MM, HSCT indications vs. "off-label" indications). The main ADRs were:

- Local reactions (infusion/injection site erythema, infusion site pain, infusion/injection site swelling, infusion site pruritus, infusion site bruising, infusion site mass)
- Hypersensitivity reactions (pruritus, rash)
- General or nonspecific reactions (headache, fatigue, nausea, pyrexia, pain, diarrhoea, vomiting, malaise, chills)
- Events consistent with patient's underlying immunodeficiency conditions (sinusitis, pneumonia, bronchitis, upper respiratory tract infection, nasopharyngitis)

Detailed information is required regarding the reported 50 fatal SID cases. The MAH informed about 50 cases with fatal outcome, thereof 45 cases from a patient support program. Thirty of these were consumer cases, non-HCP-confirmed. For the remaining 15 cases, the MAH was asked to provide proportion of cases, which were un-assessable due to missing information as well as the proportion of cases not related or unlikely, related due to the assumption that underlying disease being a more plausible explanation for the cause of death. Detailed information was requested for those fatal cases that may be related to the treatment with Hizentra. In response to OC, the MAH provided information on the 50 SID fatalities as requested.

On review of the CIOMS Reports, we concur with the evaluation of the MAH: either relevant information on the fatalities is missing or in those cases where more data is provided, there does not seem to be a direct correlation with Hizentra treatment.

The MAH provided further information on the 15 non-HCP-confirmed fatal cases from a patient support program:

Cases unassessable due to missing information: 11/15 (73%)

Cases not related or unlikely related due to another, more plausible, explanation for death: 4/15 (17%)

The MAH states that there were no fatal cases considered by the company or reporter to be related to Hizentra: 0/15 (0%).

Of note, no detailed information on the death of an 11-year old female (non-HCP-confirmed) receiving Hizentra for treatment of SID was reported. The issue wasn't further pursued.

2.5.2. Conclusions on clinical safety

Given the totality of the dataset (literature review and post-marketing analysis of patients with SID receiving IgPro20), one can conclude that the product is overall well tolerated and safe and that the safety profile of Hizentra as described in the submitted SmPC is acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Local Reactions including ulceration like-infusion site reactions (UL-ISRs) • Anaphylactic reactions • Aseptic Meningitis Syndrome (AMS) • Thromboembolic events (TEE)
Important potential risks	• Increased or unknown risks in the home-based SC (self-) administration • Exacerbation of existing hyperprolinemia • Haemolysis • Transmission of infectious agents
Missing information	• None

AMS = aseptic meningitis syndrome; SC = subcutaneous; TEE = thromboembolic event; UL-ISR = ulceration like-infusion site reaction.

Pharmacovigilance plan

There are no additional pharmacovigilance activities which are required to address safety concerns or to measure the effectiveness of risk minimization measures.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Local reactions including UL ISRs	Routine risk minimization measures: Undesirable effects section of the global RSI Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Anaphylactic reactions	Routine risk minimization measures: Undesirable effects, Contraindications, and Warnings & precautions for use sections of the global RSI Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None
AMS	Routine risk minimization measures: Undesirable effects and Warnings & precautions for use sections of the global RSI Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None
TEE	Routine risk minimization measures: Undesirable effects and Warnings & precautions for use sections of the global RSI Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None
Important potential risks		
Increased or unknown risks in the home-based SC (self-) administration	Routine risk minimization measures: Information on method and route of administration: Posology & method of administration and Warnings & precautions for use sections of the global RSI Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Exacerbation of existing hyperprolinemia	Routine risk minimization measures: Contraindications section of the global RSI Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hemolysis	Routine risk minimization measures: None Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None
Transmission of infectious agents	Routine risk minimization measures: Warnings & precautions for use section of the global RSI Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None

AMS = aseptic meningitis syndrome; global RSI = global reference safety information (company core data sheet); SC = subcutaneous; TEE = thromboembolic event; UL-ISR = ulceration like-infusion site reaction.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of MS Slovenia and Northern Ireland.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SID constitutes a large number of conditions resulting from immune system compromise due to a non-genetic factor, differentiating it from PID. SID is an umbrella term for variety of diseases with secondary immune defects, including hematologic malignancies, HIV infections, prematurity, hypogammaglobulinemia associated with solid organ or bone marrow transplantation, patients who have received B-cell–depleting agents for therapy, and protein-losing conditions.

3.1.2. Available therapies and unmet medical need

Currently, treatment of primary diseases that cause SID includes antibiotics, steroids, chemotherapy, and monoclonal antibodies. IgRT administered via either IVIG or SCIG routes is the mainstay treatment to prevent or reduce the frequency and severity of infections in patients with PID or SID.

3.1.3. Main clinical studies

The MAH provided an overview of the literature regarding SCIG use in SID (the main studies were selected by the assessor – only IVIG studies or case reports were not included in this assessment)

Trials performed with Hizentra (IgPro 20) in SID encompassed:

- Vacca et al 2018, performed a prospective, controlled, randomised 18 month study in 46 multiple myeloma (MM) patients (24 on IgPro20 and 22 controls) with IgG <500 mg/dL who received a monthly total dose of 0.4 to 0.8 g SCIg/Kg. Various patient

- Campagno et al, 2014, performed a single centre, retrospective study in 61 patients with rituximab-related SID.

- Shankar et al 2013, did a retrospective analysis of the efficacy and tolerability of subcutaneous immunoglobulin replacement on 10 lung-transplant recipients

- Spadaro et al 2016, perfomed a non-randomised cross-over study in 14 patients with a B-cell lymphoproliferative disease (12 with NHL and 2 with CLL)

Trials with SCIG /IVIG either without Hizentra, or where the brand is not mentioned:

- Dimou et al 2018; did a retrospective single centre study, in 33 SID patients with haematological malignancies were treated with HyQvia, 13/33 were already on IVIG before switching.

- Reiser et al 2017; the SIGNS study was a prospective, long-term (FU 3y/pt) non-interventional study (NIS) (ClinicalTrials.gov: NCT01287689). Forty-eight centres throughout Germany enrolled 307 SID patients (CLL, MM, indolent lymphoma, and other malignancies such as non-Hodgkin lymphoma or HIV). Particular focus of the study was the annual SBI rate.

- Benbrahim et al 2019; this was a non-interventional, longitudinal, prospective French study (21 sites) in 160 patients starting IgRT (octagam (IVIG) and gammanorm (SCIG)) for hematological malignancies associated with SID.

In keeping with the other data, lgRT increased serum IgG levels (by 3.4±2.4 g/L) and decreased frequency and severity of infections compared to baseline. Overall, the products octagam or gammanorm were well-tolerated.

3.2. Favourable effects

SCIG is currently approved for use in SID indications of CLL, MM, and HCST. Although the clinical aspects of the underlying disorders in both on-label and off-label indications differ, the SID symptoms as they are derived from insufficient or dysfunctional IgG resulting in an increased rate of infections. Therefore, an extension of indication to cover other disorders leading to SID (as is already implemented for IVIG) is seen as acceptable.

All studies mentioned above (*Summary of main studies*) showed increases in IgG trough levels and/or reduction in infection rates after receiving IgRT for SID. This was shown for Hizentra but also for other SCIGs. The results are comparable to those seen with IVIG treatment.

While IVIG and SCIG are both recommended as IgRT, SCIG allows patients to self-treat at home and thus provides greater independence from the need for frequent hospital or infusion clinic visits. In addition, administration of IVIG can be difficult in patients with poor venous access- a problem avoided when SCIG is used.

3.3. Uncertainties and limitations about favourable effects

Although there are not per se any uncertainties as to the favourable effects of IgRT treatment in SID patients, certain limitations arise from the data provided, concerning the optimal dosing. Some studies suggest that lower dosing (~ 300 mg/kg/month) could also lead to a reduction in infection rate; other studies mention "drug holidays" in the summer months when the risk of infections spontaneously decreases. However, as the Hizentra SmPC outlines a broad range of possible doses for both PID and SID, this is currently acceptable.

3.4. Unfavourable effects

The unfavourable effects are outlined in the SmPC and are adjusted according to PSUSA evaluations.

They mainly concern:

- Local reactions (infusion/injection site erythema, infusion site pain, infusion/injection site swelling, infusion site pruritus, infusion site bruising, infusion site mass) as well as infusion site necrosis in rare cases.
- Hypersensitivity reactions (pruritus, rash)
- General or nonspecific reactions (headache, fatigue, nausea, pyrexia, pain, diarrhoea, vomiting, malaise, chills)
- Events consistent with patient's underlying immunodeficiency conditions (sinusitis, pneumonia, bronchitis, upper respiratory tract infection, nasopharyngitis)

50 SID cases with a fatal outcome have been reported. Thirty of these were consumer cases, non-HCP-confirmed. For the remaining cases, the MAH was requested to provide detailed information, especially for those fatal cases that may be related to the treatment with Hizentra. Data was provided and considered adequately addressed by the CHMP.

3.4.1. Importance of favourable and unfavourable effects

In CLL up to 80% of CLL patients experience infectious complications at some point during their disease, 20% of them severe/major infections. Up to 60% of overall mortality in CLL is caused by infectious complications. In a study of more than 3,000 patients with multiple myeloma, infections were responsible for 45% of deaths within 6 months of diagnosis. In CLL and MM and in the setting of SID from other underlying disorders the risk of recurrent and possibly life-threatening infections can be alleviated by the administration of either IVIG or SCIG. This is clinically important.

The unfavourable effects of SCIGs are well-known and described in the SmPC; they mainly concern infusion site reactions and to a lesser extent general reactions (e.g. headache, fatigue, nausea, pyrexia, pain, diarrhoea, vomiting, malaise, chills). In most cases, these ADRs are mild to moderate and can in persistent cases be alleviated with pre-medication. Some severe cases of either local or general reactions may attain clinical importance.

3.4.2. Balance of benefits and risks

Given the totality of the data, the balance of efficacy to safety is positive

3.5. Conclusions

The overall B/R of Hizentra is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to expand the approved secondary immunodeficiencies (SID) indications to any symptomatic SID in accordance with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/ 2007 Rev 5; CHMP, 2018). As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.6 of the RMP has been accepted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA/H/C/002127/II/0129'