CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Normal Immunoglobulin (Human) 10% and Recombinant Human Hyaluronidase (HyQvia)

Indication: As replacement therapy for primary humoral immunodeficiency and secondary humoral immunodeficiency in adult patients.

Sponsor: Takeda Canada Inc.

Recommendation: Reimburse with Conditions

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CADTH

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CADTH

NORMAL IMMUNOGLOBULIN (HUMAN) 10% AND RECOMBINANT HUMAN HYALURONIDASE (HYQVIA — TAKEDA CANADA INC.)

Therapeutic Area: Humoral immunodeficiency

Recommendation

The CADTH Canadian Plasma Protein Product Expert Committee (CPEC) recommends that normal immunoglobulin (human) 10% and recombinant human hyaluronidase (IgHy10) be reimbursed as replacement therapy for primary humoral immunodeficiency and secondary humoral immunodeficiency in adult patients only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, open-label, non-randomized, single group, prospective studies (Study 160603, [N = 89], and related extension study, Study 160902, [N = 66]) demonstrated that treatment with IgHy10 resulted in clinical benefit for patients with primary immunodeficiency (PID) requiring immune globulin replacement therapy. The rate of validated acute serious bacterial infections (VASBI) was less than 1.0 infections per patient per year in both studies ($P < 0.0001$). Direct comparative evidence for IgHy10 versus current immune globulin replacement therapies was not identified, which is a significant limitation of the available evidence, but infectious outcomes observed are consistent with other immune globulin replacement therapies currently utilized in Canada. Patients and clinical experts both identified the need for a treatment that would reduce bacterial infections and maintain consistent IgG serum levels, that also minimizes disruptions to the lives of patients through the ability to administer treatment less frequently compared to conventional subcutaneous immune globulin (cSCIG) and outside of the hospital setting compared to intravenous immune globulin (IVIg). The available evidence, including post-marketing studies, suggests that IgHy10 has the potential to address these needs in some patients. In addition to the clinical benefit demonstrated in studies 160603 and 160902, additional evidence and expert opinion suggested that IgHy10 may result in fewer infusions required compared to cSCIG for those patients who can self-administer at home, where improved health-related quality of life (HRQoL) and adherence might be anticipated. Other needs identified by patients included improving HRQoL and tolerability; while evidence to support improved HRQoL is not available, the prospective, post-marketing, and other observational studies suggest most patients tolerate IgHy10.

Using the sponsor submitted price for IgHy10 and publicly listed prices for all other drug costs, IgHy10 was more costly compared with intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg) therapies and in the cost-minimization analysis, considered similarly effective. However, there is no direct or indirect evidence that IgHy10 is clinically superior to other IVIgs and SCIgs currently reimbursed for the treatment of PID or secondary immunodeficiency (SID). As such, IgHy10 should be no more costly than the least costly IVIg or SCIg reimbursed for the treatment of PID or SID.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. Eligibility for reimbursement of IgHy10 should be based on the criteria currently used for reimbursement of other IgRT for the treatment of primary humoral immunodeficiency and secondary humoral immunodeficiency.	There is no direct or indirect evidence that IgHy10 is clinically superior or inferior to other IgRT treatments currently reimbursed for the treatment of primary humoral immunodeficiency and secondary humoral immunodeficiency.	–
Renewal		
2. Renewal criteria of IgHy10 should be based on the criteria currently used for other IgRT currently reimbursed for the treatment of primary humoral immunodeficiency and secondary humoral immunodeficiency.	There is no evidence that IgHy10 should be held to a different standard than other reimbursed options when considering renewal.	–
Prescribing		
3. IgHy10 should be prescribed by a specialist with appropriate knowledge and training in primary humoral immunodeficiency and secondary humoral immunodeficiency.	Accurate diagnosis and follow-up of patients with primary humoral immunodeficiency and secondary humoral immunodeficiency are important to ensure that IgHy10 is prescribed to the most appropriate patients. In addition, there are several IgRT treatment options that may be considered when selecting the most appropriate therapy for patients; these are best determined by immunologists, rheumatologists, or hematologists with training in IgRT.	CPEC noted that ideally, the prescription should be performed by an immunologist and/or appropriate specialty physician with training in IgRT. However, many patients in remote centres may not have immediate access to those physicians and prescriptions may need to occur via non-specialized physicians who have consulted with specialty physicians. An appropriate specialist must prescribe the drug, but patients with difficult access to care (for example, patients living in remote areas) can be monitored or followed by other clinicians under the guidance of the specialist.
Pricing		
4. The price of IgHy10 should be negotiated so that it does not exceed the drug program cost of treatment with the least costly IVIg or SCIg reimbursed for the treatment of primary humoral immunodeficiency and secondary humoral immunodeficiency.	There is no direct or indirect evidence that IgHy10 is clinically superior to other IVIg or SCIgs currently reimbursed for the treatment of primary humoral immunodeficiency and secondary humoral immunodeficiency. As such, there is insufficient evidence to justify a cost premium for IgHy10 over the least expensive IVIg or SCIg reimbursed for adults with primary humoral immunodeficiency and secondary humoral immunodeficiency.	
Feasibility of Adoption		

Reimbursement Condition	Reason	Implementation Guidance
5. The feasibility of adoption of IgHy10 must be addressed	At the submitted price, the budget impact of IgHy10 is expected to be greater than $40 million in years 1, 2, and 3. Furthermore, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	

CPEC = Canadian Plasma Protein Product Expert Committee; IgHy10 = normal immunoglobulin (human) 10% and recombinant human hyaluronidase; IgRT = immunoglobulin replacement therapy; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.

Discussion Points

- CPEC acknowledged that the therapeutic component of IgHy10, normal human immunoglobulin (10%) (Gammagard Liquid), is analogous to other IgRTs currently available in Canada for the treatment of patients with PID and SID. In addition, the clinical experts noted to CPEC that the rate of VASBI observed in the pivotal trials of IgHy10 was similar to other IgRTs currently utilized in Canada.
- CPEC acknowledged that IgHy10 offers potential ancillary clinical benefits for patients with PID or SID in having fewer infusions compared to cSCIG and recognized the similarities to other immune globulin replacement therapies in clinical benefit for reducing infections despite the limitations of Study 160603 and Study 160902, including the lack of randomization and high study discontinuation rates.
- In Study 160603, only 20.5% of all infusions were administered at home without nurse intervention. In Study 160902, 64% of patients and 52% of infusions required assistance and were unable to continue self-administration of infusions at home. The clinical experts and post-marketing data suggest to CPEC that, in practice, the proportion of patients who might be able to manage their condition with infusions at home is likely higher than what was reported in the studies. Additionally, the clinical experts noted that the ability to successfully self-administer IgHy10 at home depends on the ability to complete training for home infusion, which must be considered along with the use of IgHy10 as patients who are unable to complete this training may be better served by IVIg or cSCIg. CPEC acknowledged that IgHy10 offers an additional treatment option with the potential to be self-administered at home.
- CPEC discussed that determination of whether the patient would be a good candidate for treatment with IgHy10 should be at the discretion of both the treating clinician and patient. No literature or data informs a particular patient population that would benefit from IgHy10.
- CPEC discussed that each province or territory will likely have different approaches to IgRT utilization management; therefore, renewal criteria should align with the jurisdictional guidelines.
- No direct or indirect evidence was available comparing the efficacy or safety of IgHy10 with other immunoglobulin replacement therapies (IgRTs) used for patients with primary humoral immunodeficiency and secondary humoral immunodeficiency. CPEC identified this as a significant evidence gap and was unable to determine the potential clinical benefits of IgHy10 compared with other available IgRTs. As such, the evidence does not support a price premium over currently available IgRTs for adults with primary humoral immunodeficiency and secondary humoral immunodeficiency.

Background

Primary immunodeficiency disorders or inborn errors of immunity encompass a heterogeneous group of disorders that are genetically determined, resulting from inherited defects in the development and/or function of the immune system. An estimated 1 in 1,200 Canadians live with PID, with over 70% of patients remaining undiagnosed. The drug under review is indicated for the treatment of humoral immunodeficiencies, which result from B-cell defects that lead to antibody deficiencies and account for 50 to 60% of PIDs. Living with PID predisposes affected people to an increase in the frequency and severity of infections, autoimmunity, and aberrant inflammation and malignancy. The presentation of PIDs can occur at any age, and patients with B-cell (antibody-deficiency) disorders typically present after 6 months of age with recurrent and often severe sinopulmonary infections such as otitis media, sinusitis, and

pneumonia, and gastrointestinal infections. Diarrhea, fatigue, autoimmune manifestations (such as autoimmune cytopenia), and hearing loss are also common. Secondary immunodeficiencies are acquired and much more common than PIDs. They may result from systemic disorders, immunosuppressive treatments, or prolonged serious illness. Additionally, patients who are critically ill, older, or hospitalized are susceptible to acquired or SID. Secondary humoral immunodeficiency is a type of SID that occurs across a wide spectrum of diseases with a range in the level of susceptibility to infection and can sometimes be reversed. An estimation of the prevalence and incidence of SID or secondary humoral immunodeficiency in Canada was not identified; however, a study by Patel et al. (2019) reported that secondary humoral deficiencies are estimated to be 30-fold more common than primary humoral immunodeficiencies.

Human immunoglobulin preparations for intravenous or subcutaneous administration, or IgRT, are the cornerstone of treatment in patients with immunodeficiencies affecting the humoral immune system. The clinical experts consulted by CADTH indicated that it is important to note, that not only patients with predominantly antibody deficiencies, but with other forms of PIDs, such as combined immunodeficiencies or inborn errors of immunity, also might require long term or even lifelong IgRT. Both IVIg and SCIg therapies have limitations, one of which is associated adverse events (AEs). Adverse events associated with SCIg tend to be local reactions, whereas systemic AEs are more commonly reported with IVIg. Other reasons for using SCIg include: improved consistency of IgG serum levels (less of a difference between peak and trough levels), administration may be performed at home, and no requirement for venous access. Disadvantages of SCIg compared to IVIg include a higher frequency of infusions and a requirement for multiple injection sites, as well as compliance for some patients. Treatment with IVIg allows for administration of larger volumes of IgG compared to SCIg, more frequent and direct contact with healthcare professionals, and less frequent administration. In addition to IgRT, early and aggressive treatment of infections with antimicrobial agents is essential in patients with several forms of inborn errors of immunity, including primary humoral immunodeficiency. Non-drug therapies for the treatment of humoral immunodeficiencies include avoidance of some live vaccines for selected diseases, and close monitoring and co-treatment for comorbidities including autoimmune diseases (cytopenias, enteropathies, celiac disease, thyroid disease, granulomas), respiratory status and function, and malignancies.

Normal immunoglobulin (human) 10% and recombinant human hyaluronidase (IgHy10) has been approved by Health Canada as replacement therapy for primary humoral immunodeficiency and secondary humoral immunodeficiency in adult patients. IgHy10 is an immunoglobulin replacement therapy. Both components of IgHy10 are provided as solutions for subcutaneous infusion and the dosage recommended in the product monograph for IgHy10 varies by previous treatment experience, as follows:

- Patients naïve to IgG treatment should receive IgHy10 at 300 to 800 mg/kg at 3- to 4- week intervals, after initial ramp-up, and adjust as necessary based on IgG levels and clinical outcome.
- Patients that were previously treated with intravenous immunoglobulin (IVIg) or have a previous IVIg dose that can be referenced should receive IgHy10 at the same dose and same frequency as their previous IVIg treatment. When switching from IV treatment, IgHy10 is started 1 to 2 weeks after the last IV dose. If patients were previously on a 3-week dosing regimen, increasing the interval to 4 weeks can be accomplished by administering the same weekly equivalents.
- Patients previously treated with SCIg should receive an initial dose of IgHy10 at the same dose as their previous SCIg treatment, but administration may be adjusted to a 3- or 4-week interval. The first infusion of IgHy10 should be given one week after the last treatment with the previous immune globulin.

The Health Canada-approved dose of hyaluronidase is a minimum of 75 U per gram of IgG.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 2 open-label, non-randomized, single group, prospective studies in patients with a primary immunodeficiency (PID) disorder that required antibody replacement therapy
- Patients' perspectives gathered by 1 patient group, Canadian Immunodeficiencies Patient Organization (CIPO)
- Input from public drug plans that participate in the CADTH review process

- Input from 2 clinical specialists with expertise diagnosing and treating patients with primary humoral immunodeficiency and secondary humoral immunodeficiency
- Input from 2 clinician groups, the Clinical Immunology Network-Canada and the Medical and Scientific Advisory Committee of the Canadian Immunodeficiencies Patient Organization (CIPO).
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Information for the patient group submission by CIPO was collected through an online survey of patients and caregivers (N = 246) and semi-structured telephone interviews with patients (N = 8) living with PID. A total of 233 (95%) survey respondents were patients living with PID, and 13 (5%) were caregivers responding on behalf of patients. The telephone interviews were with patients currently receiving immunoglobulin replacement therapy (IgRT) for PID. None of the patients captured in the patient group submission had experience with IgHy10.

The patient group submission described living with PID as being prone to a wide range of infections that are often severe, chronic, and debilitating. According to CIPO, the frequency of infections is dramatically reduced with IgRT. As many patients with PID require lifelong therapy, the method of administration and setting where the treatment is administered are important factors that can significantly affect HRQoL. The patient preference is strongly considered when selecting SCIg or IVIg therapy, along with the efficacy of the specific therapy.

According to CIPO, patients want a treatment that minimizes disruptions to career or personal life. It was noted that administering therapy at a lower frequency and reducing the need to travel to an infusion clinic would help minimize disruption to everyday life as well as reduce the risk of hospital-acquired infections. Telephone interview respondents indicated a curiosity about trying IgHy10, but also described a desire for the same result from treatment, concerns about having a negative experience due to switching therapies, and whether IgHy10 it would be an appropriate treatment option for the individual patient seeking treatment.

Clinician input

Input from clinical experts consulted by CADTH

The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of PID and SID in pediatric and adult patients.

The clinical experts stated that treatments for primary humoral immunodeficiency that reverse the course of disease are limited. The experts also noted that treatments for secondary humoral immunodeficiency are limited, but that some etiologies can be reversed. Current options for IgRT are effective, but the clinical experts noted there is a need for treatment options that improve adherence and convenience. The clinical experts indicated that current treatments are time consuming and can negatively affect daily function due to the duration and/or frequency of administration, as well as the need to administer IVIg in a hospital setting. The clinical experts also expressed a need for treatments that are better tolerated, noting IVIg is associated with side effects including headaches, myalgia, arthralgia, and nausea, and requires premedication with antipyretics and antinausea agents. Some patients were also reported as having experienced transient acute kidney injury, aseptic meningitis, thrombotic and hyperviscosity related side effects, and fever. Lastly, the experts reported that not all patients respond to currently available IVIg and conventional SCIg (cSCIg) treatments, and that it is difficult to achieve target levels of immunoglobulin in selected patients with IVIg due to its pharmacokinetics (greater variation in peaks and troughs between infusions), which can translate to suboptimal clinical control of disease.

According to the clinical experts consulted by CADTH for this review, IgHy10 would present an additional treatment option to patients, either as first line for patients who were expected to benefit from SCIg, or as second line for those who do not tolerate IVIg

or SCIg. Both experts felt IgHy10 had potential to cause a shift in the current treatment paradigm, particularly in terms of SCIg therapies, as it would expand options for IgRT for patients with primary humoral immunodeficiency and secondary humoral immunodeficiency.

The clinical experts indicated patients who are expected to benefit from SCIg or IVIg are also expected to benefit from treatment with IgHy10. The clinical experts also indicated that patients who are expected to benefit most from switching from IVIg to treatment with IgHy10 include patients with certain comorbidities, those with limited access to health care facilities, those who had severe adverse effects to IVIg, have difficult venous access, or those who prefer not to miss school/work to receive treatment. The clinical experts also noted that patients that are likely to benefit from switching from cSCIg to IgHy10 include those who require large doses/volumes due to higher body weight or for the need for immunomodulation, those who have needle phobia and want to avoid using multiple injection sites, those who want to infuse SCIg less frequently, or those who are unable to adhere to weekly SCIg infusions.

Patients identified by the clinical experts as being least suitable for treatment included those who have little to no subcutaneous tissue (very low body fat) or severe skin conditions preventing the subcutaneous administration. The clinical experts also felt that complex patients that require frequent clinical and Ig monitoring and regular in-person re-assessment (potentially coordinated with other IV treatments) would be less suitable for treatment with IgHy10. Lastly, the clinical experts noted patients with a history of poor adherence to treatment, inappropriate compliance, or inappropriate support from a caregiver (particularly for pediatric patients) may also be less suitable for treatment with IgHy10.

The clinical experts indicated that patients with primary or secondary humoral immunodeficiency starting treatment with IgHy10 who also have chronic or active infections are expected to respond to treatment with an improvement in clinical state and normalized blood IgG levels (IgG target levels achieved). The clinical experts described long-term expectations for response to treatment as a reduction in frequency and severity of infections, which should result in fewer visits to outpatient clinics, a reduced rate of emergency visits and/or hospitalizations due to infections, reduced need for antimicrobial treatments or prophylactic use, fewer missed days from school or work, and improved overall health and HRQoL. The experts would also expect the overall burden experienced by caregivers and by the health care system to be reduced.

The experts described a clinically meaningful response to treatment as one that would include maintenance of target steady-state serum IgG trough levels (at least 7 g/L), reduced infection rate (no serious infections or significantly less severe infections per year), no ER visits or hospital admissions due to infections, significant reduction in days missed from work or school, improved survival and HRQoL, and remission of autoimmune and inflammatory diseases associated to inborn error of immunity if present. Further, the experts noted that all of these outcomes are clinically meaningful when achieved without serious adverse events (SAEs).

The clinical experts suggested that patients treated with IgHy10 should be assessed for response to treatment every 3-6 months depending on the disease severity, which is consistent with current clinical practice of patients with PID/SID.

Feedback from the clinical experts indicated that discontinuation of treatment with IgRT would be considered if there is a lack of improvement in Ig replacement levels, or if response to treatment (as described above) is not achieved despite increasing doses of IgRT. The experts also noted that issues with adherence (identified by an inability to maintain therapeutic serum IgG levels) may result in discontinuation from IgHy10 as they may be better served by IVIg. Discontinuation from IgHy10 may also be considered based on patient preference, or for patients who do not exhibit an improvement in HRQoL, as described by the clinical experts.

According to the clinical experts, IgHy10 can be administered at home after appropriate training by a patient support program, similar to current practice for other SCIg preparations. The experts also noted that select cases may warrant infusion of IgHy10 in a health care facility (infusion clinic, outpatient clinic, in hospital medical day treatment unit), such as when the caregiver/patient is unable to administer the infusion. The experts indicated that a specialist with appropriate knowledge and training in PID/SID should be involved in the diagnosis and initiation of therapy. This may include Immunologists, Rheumatologists, and Hematologists with training in IgRT.

Clinician group input

Seven clinicians authored two clinician group input submissions on behalf of two clinician groups: the Clinical Immunology Network-Canada and the Medical and Scientific Advisory Committee of the Canadian Immunodeficiencies Patient Organization. The clinician group input was aligned with the input provided by the clinical experts consulted by CADTH, with the exception of place in therapy

and assessment of treatment response, which differed slightly. The clinician groups felt that IgHy10 would likely be used as a second-line treatment (following IVIg or cSCIg) for primary or secondary humoral immunodeficiency in general, but could become a first-line treatment option in certain subpopulations of patients with the greatest unmet need. The clinician group input recommended treatment response be assessed at least every 6 to 12 months, which is longer than the frequency of 3 to 6 months suggested by the clinical experts consulted by CADTH. The clinician groups also noted that there are considerable benefits associated with the ability to treat patients at home, particularly in terms of rising capacity issues for both inpatient and outpatient beds and the increasing costs of medicines.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
Does IgHy10 allow a similar dose as IVIg and potentially lower dose than cSCIg per patient? If a patient is switched from IVIg/cSCIg to IgHy10, how much would the dose be expected to change?	Similar to the other cSCIg products, the IgHy10 dose is calculated as it would be for IVIg dosing and administered similarly every 4 weeks. A change in the dose or dosing interval is not expected for a switch from IVIg to IgHy10. When switching from SCIg to IgHy10, the monthly dose would be the same and the dosing interval is extended to every 3 or 4 weeks. For example, a patient on 40g/month dose of IVIg would give 10g every 7 days of cSCIg or 40g every 28 days of IgHy10. Therefore, a switch from SCIg and IgHy10 is not expected to result in a change to monthly dose, but the dosing interval would be adjusted as described. Of note, IgHy10 dosing in Study 160603 and 160902 was 108% of the dose of IVIg received during Epoch 1 of Study 160603. CPEC agreed with the response provided by the clinical experts.
How does IgHy10 compare with IVIg and cSCIg in terms of safety? a) Sponsor claims that recombinant hyaluronidase allows greater dispersion and absorption of Ig in a tissue. Does IgHy10 require fewer infusion sites than cSCIg for administration because of recombinant hyaluronidase? Does this translate into lesser local side effects? b) IgHy10 has lower peak-to-trough variation than IVIg and slightly higher than cSCIg. Does this translate into lesser/higher systemic adverse events?	At the time of this review, no evidence comparing treatment with IgHy10 with other forms of IgRT (IVIg or cSCIg) was identified. Based on the results presented in Study 160603 and Study 160902, the clinical experts felt that similarly to other cSCIg products, IgHy10 appears to translate to more local but fewer systemic adverse events than what is observed with IVIg treatment in clinical practice. In general, CPEC agreed with the responses provided by the clinical experts, but also noted that IgHy10 presented with more systemic adverse events than what is observed in clinical practice with other SCIg.
What is the average dosing interval of IgHy10 and how does it compare with IVIg and cSCIg?	The clinical experts consulted by CADTH do not have experience using IgHy10 in clinical practice; however, cSCIg can be administered at intervals of up to every 2 weeks. CPEC agreed but noted that the typical dosing interval for cSCIg tends to be weekly. The clinical experts also stated and CPEC agreed that based on the literature, the average dosing interval of IgHy10 is expected to be greater than cSCIg, reaching up to every 3 or 4 weeks. This is consistent with the dosing interval used for IVIg in clinical practice.
How does IgHy10 compare with other Ig brands in terms of overall infusion time?	Individual IgHy10 infusion times are expected to be shorter compared to the same dose of IVIg, and longer compared to cSCIg. This is because with cSCIg, patients infuse smaller

Implementation Issues	Response
	volumes administered more frequently. CPEC agreed with this response from the clinical experts. For reference, in Study 160603, the median duration of IVIg infusion was 2.33 hours (range = 0.92 to 6.33) and the median duration of IgHy10 infusion was 2.08 hours (range = 0.83 to 4.68).
Considerations for Initiation of Therapy	
If IgHy10 is found to be more costly than other Ig brands for not much benefit, we would need clear criteria on when IgHy10 should be considered over other immunoglobulin brands, for example, should patients with treatment compliance issues with cSCIg or unable to tolerate it be eligible for IgHy10? Should patients with poor venous access and unable to use IVIg be eligible for IgHy10?	The clinical experts indicated that they would consider the use of IgHy10 for patients that they would consider cSCIg for. This would include patients with poor venous access as well as patients with tolerability or compliance issues with cSCIg. CPEC agreed with the response provided by the clinical experts.
Considerations for prescribing of therapy	
What percentage of patient population would be able to manage their condition at home with monthly frequency?	Again, the clinical experts consulted by CADTH do not have experience with IgHy10; however, they would expect the proportion of patients who are able to manage their condition with cSCIg at home to be similar to IgHy10, i.e. more than 90% of patients. Overall, CPEC agreed with the response from the clinical experts, but noted the discrepancy between what was expected and what the clinical trial results were.
IgHy10 is a dual vial unit. It has the same route but different administration method than cSCIg. What level of special training would patient/caregiver needs to be comfortable administering IgHy10?	A specialized training program (such as OnePath Program in case of another cSCIg product) would be essential to help orient patients to the administration of IgHy10 as well as educate patients on possible adverse events and how to treat them. The support program could also help navigate access issues. It was recommended that education around mechanism of action of IgHy10 be included. Additionally, the program should be continuously available to support patients on IgHy10. CPEC also noted that the prescriber should also be available to support patients on IgHy10. The clinical experts felt the current capacity of training programs for SCIg products would likely not need to be increased, but the duration of training sessions would likely need to be increased by approximately 15-30 minutes. IgHy10 infusion would require slightly more training than cSCIg products. The clinical experts felt that more than 90% of patients would be able to successfully complete training to be able to comfortably administer IgHy10 at home. CPEC felt the responses from the clinical experts were reasonable.
If a patient starts IgHy10, can they switch to other Ig brands during the course of treatment?	The clinical experts and CPEC would not expect to have any issues with switching patients on IgHy10 to other brands of IgRT. CPEC also noted that they would not expect issues with switching patients on IgHy10 to other types of IgRT, for example, IVIg may be a more appropriate treatment depending on the circumstances that lead to the desire to switch treatments.
Care provision issues	

Implementation Issues	Response
Is there any additional monitoring required or safety concerns due to administration of recombinant hyaluronidase?	The clinical experts and CPEC did not express any safety concerns or additional monitoring for administration of IgHy10.

CPEC = Canadian Plasma Protein Product Expert Committee; cSCIg = conventional subcutaneous immunoglobulin; IgHy10 = normal immunoglobulin (human) 10% and recombinant human hyaluronidase; IgRT = immunoglobulin replacement therapy; IVIg = intravenous immunoglobulin; PID= primary immunodeficiency; SCIg = subcutaneous immunoglobulin; SID = secondary immunodeficiency.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

Two sponsor-submitted, phase III, open-label, non-randomized, single group, prospective studies were included in this review. The pivotal study, Study 160603 (N = 89), evaluated the efficacy and tolerability of IgHy10 in patients that were at least 2 years of age with a PID disorder that required antibody replacement therapy. Patients were also required to have a serum trough level of IgG greater than 4.5 g/L and to have been receiving regular IgRT for at least 3 months prior to enrolment. Study 160902 (N = 66) was an extension of Study 160603 that evaluated the long-term tolerability and safety of IgHy10. The safety extension also followed patients after discontinuation of hyaluronidase for delayed adverse reactions.

Study 160603 consisted of two epochs. During Epoch 1, patients received IVIg 10% for 12 weeks. Of the 89 patients that were enrolled in Epoch 1, 87 (98%) received IVIg treatment. Subsequently, 83 (93%) of the patients from Epoch 1 continued to Epoch 2 where patients received IgHy10 (75 U/g recombinant hyaluronidase followed by SCIg 10%), administered at 108% of the monthly total IVIg dose every 3 or 4 weeks, for 14 to 18 months. The primary endpoint in Study 160603 was acute serious bacterial infection rate, defined as the mean number of validated acute serious bacterial infections (VASBI) per patient per year. The annual rate of all infections, IgG levels, antibiotic use, healthcare utilization, productivity, HRQoL, tolerability, and safety were also evaluated.

Patients in Study 160603 that were exposed to treatment had a median age of 35.0 years (range = 4 to 78), were primarily White (91%) and non-Hispanic or -Latino (91%), and 51% were male. The most commonly diagnosed PID among patients was common variable immune deficiency (56%), followed by hypogammaglobulemia (20%) and X-linked agammaglobulinemia (7%). All patients reported a medical history including disorders of the hematopoietic/lymphatic system, and the majority also reported medical conditions relating to the eyes, ears, nose and throat (98%) and respiratory system (87%). The median serum IgG trough levels up to 6 months before enrolment were 10.34 g/L (range = 4.05 to 32.00). There were no notable differences in the demographic characteristics of patients who continued into Extension Study 160902.

Efficacy Results

The efficacy results have been summarized with a focus on the results reported during Epoch 2 of Study 160603, when patients were treated with IgHy10. It is important to note that in Study 160603, treatment with IgHy10 (Epoch 2) cannot be compared to treatment with IVIg (Epoch 1) as the study was not designed to assess this.

Infections

The primary endpoint of Study 160603 was analyzed based on the null hypothesis of one or more VASBI per patient per year tested against the alternate hypothesis of less than 1 VASBI per patient per year, as per regulatory guidance from the FDA. Comparisons of IgHy10 to other IgRT were not available. A total of two VASBI were reported during treatment with IgHy10 in Epoch 2; both cases were episodes of bacterial pneumonia that were treated with oral antibiotics without hospitalization. This corresponded to a rate of 0.025 VASBI per year [upper limit of the 99% confidence interval (CI), 0.046]. The clinical experts on this review agreed that the reported rate of VASBI was aligned with what would be expected from an IgRT treatment. The rate of VASBI was not reported during treatment with IVIg in Epoch 1. The rate of VASBI per year prior to the safety follow-up period was similar among the 66 patients that continued to extension Study 160902 (0.020; upper limit of the 99% CI, 0.045).

In Study 160603, the rate of all infections reported during treatment with IVIg in Epoch 1 was 4.51 infections per year (95% CI, 3.50 to 5.69). During treatment with IgHy10 in Epoch 2, the rate of all infections was 2.97 infections per year (95% CI, 2.51 to 3.47). In the extension Study 160902, the rate of all infections during treatment with IgHy10 was 2.86 infections per year (95% CI, 2.36 to 3.43).

Additionally, Wasserman et al. (2016) evaluated in a post-hoc analysis patients from Study 160603 and Study 160902 from the first administration of IgHy10 through the end of treatment. The annual rate of infections and annual rate of VASBIs during IgHy10 treatment were reported by age group (< 18 and ≥ 18 years). For patients that were at least 18 years of age (n = 59), the rate of infections was 2.98 per year (95% CI, 2.56 to 3.44) and the rate of VASBIs was 0.01 per year (upper limit of 99% CI = 0.02). The rate of infections and VASBIs were consistent with the results reported for each of the individual studies.

Immunoglobulin levels

The pivotal study and extension study evaluated IgG trough levels. The clinical experts consulted by CADTH indicated that IgG trough levels were routinely assessed in clinical practice and used as an indicator for the ability to prevent infection and disease-related comorbidities. Published recommendations for treatment with IgRT suggest IgG trough levels should exceed 5 g/L and ideally be more than 7 g/L. At baseline in Study 160603, the median serum IgG trough levels were approximately 10 g/L. In patients who were at least 12 years old, the median IgG trough level was 10.70 g/L (95% CI, 9.46 to 11.80). The IgG trough levels while receiving IgHy10 during Epoch 2 appeared similar to IgG trough levels while receiving IVIg in Epoch 1.

In extension Study 160902, patients were asked to increase the frequency of IgHy10 administration to a 2-week or 3-week interval for a minimum of 4 months to evaluate the effect of varying dose intervals on IgG levels. In summary, the steady-state IgG trough levels were maintained at a median of at least 10 g/L at a dose administration interval of 2, 3, or 4 weeks. After 4 months, patients had the option of returning to their initial dose interval or stay on the 2- or 3-week interval [17/66 (25.8%) of patients stayed on a 2-week interval for more than 4 months]. The ratio of IgG trough levels measured at the end of the safety follow-up period compared to IgG trough levels measured at the end of IgHy10 treatment were also reported, which indicated that IgG levels were maintained or increased following discontinuation of hyaluronidase over a period of approximately 1.5 years (mean duration of treatment was 565.9 days, SD = 211.8). Although the clinical experts consulted by CADTH indicated that IgG levels are routinely assessed and useful as a reference point, they also noted that treatment decisions are predominantly based on clinical assessments of the patient as opposed to solely relying on laboratory values.

Antibiotic use

Outcomes related to antibiotic use was identified as an important outcome to clinicians and patients. Antibiotic use was reported as a point estimate of the number of days per month on antibiotics. Based on this, it was estimated that during treatment with IgHy10 in Study 160603, patients were on antibiotics for 1.68 days per month (95% CI, 1.29 to 2.16). In the extension study (Study 160902), the point estimate for days on antibiotics was reported annually. While receiving treatment with IgHy10 prior to the safety follow-up period, patients were on antibiotics for 64.03 days per year (95% CI, 45.16 to 87.54). The clinical experts consulted by CADTH indicated that the rate of antibiotic use was higher than expected, noting that it is atypical for patients to use antibiotics on a monthly basis. Patients who could not discontinue prophylactic antibiotic use were excluded from the trials and concomitant prophylactic antibiotic use was not permitted during the trials. This is likely to overestimate the use of antibiotics in the trials; however, the magnitude of overestimation is difficult to determine as the proportion of patients who were using antibiotics prophylactically prior to enrolment was not reported. Thus, there is significant uncertainty associated with the results for antibiotic use.

HRQoL

Health-related quality of life was evaluated in Study 160603 and extension Study 160902 using the PEDS-QL and SF-36 and reported by age group (2-7, 7-14, and at least 14 years old). Evidence of validity, reliability, and responsiveness was identified for both the PEDS-QL and SF-36; however, not in patients with immunodeficiencies. In Study 160603 using the SF-36 for patients of at least 14 years, the mental and physical summary score was a median of 52.2 (range, 21.5 to 70.8) and 44.8 (range, 13.1 to 61.1), respectively. The HRQoL results were similar in the extension study, as the mental and physical summary score was a median of 51.0 (range, 25.3 to 56.9) and 48.7 (range, 11.6 to 52.9), respectively. Although limited by methods of analysis and sample size, the evidence suggests there was no change in HRQoL following treatment with IgHy10.

Tolerability and adherence

In Study 160603, 77/87 (89%) of patients and 350/365 (96%) of infusions did not require a reduction, interruption, or stoppage of infusion due to tolerability concerns while receiving IVIg in Epoch 1. During treatment with IgHy10 in Epoch 2, 68/81 (84%) of patients and 1103/1129 (98%) of infusions did not require a reduction, interruption, or stoppage of infusion due to tolerability concerns. The findings in patients receiving treatment with IgHy10 during the extension Study 160902 were similar to what was observed in Study 160603.

One of the key advantages that was anticipated for IgHy10 was the ability to administer treatment at home, less frequently than cSCIg, thereby improving the convenience and minimizing the impact of treatment on a patient's life. The clinical experts consulted by CADTH indicated they expected the majority of patients (more than 90%) would be able to self-administer IgHy10 at home, similar to what they had observed with cSCIg in clinical practice. In Epoch 2 of Study 160603, 282/1129 (25%) of infusions were administered at home, 231 (82% of infusions at home or 20.5% of all infusions) of which were administered without nurse intervention, and the majority of IgHy10 infusions (847/1129 or 75.0%) were administered at investigational site. Infusions were required to occur at the investigational site until at least 2 infusions at the maximum infusion interval were tolerated, but the proportion of infusions this applies to is unknown based on the data available. While receiving IgHy10 (prior to the safety follow-up period) in extension Study 160902, 64% of patients and 52% of infusions required assistance with self/home-infusion. Reasons for being unable to continue self-administration of infusions at home were due to a medical reason (9/63 or 14.3% of patients), because of a family member (10/63 or 15.9% of patients), or for other reasons (37/63 or 58.7% of patients). Additional information about the reasons for being unable to self-administer infusions at home was not provided. Further, whether the ability to self-administer IgHy10 improves over time is unknown.

Healthcare utilization and productivity

Outcomes related to healthcare utilization and productivity were of importance to clinicians and patients. A point estimate of the number of acute physician visits, days in hospital, days in hospital due to infection were reported per month in Study 160603 and per year in Study 160902.

In Study 160603, patients reported an acute visit to a physician on approximately 0.40 days per month (95% CI, 0.32 to 0.49) while receiving treatment with IgHy10. There was no substantial difference in acute physician visits reported during IgHy10 (after the ramp-up) and during Epoch 1 while receiving IVIg (0.33 days per month; 95% CI, 0.23 to 0.45). The monthly rate of days in hospital and days in hospital due to infection were similar in Epoch 1 and Epoch 2, with overlapping confidence intervals for the reported point estimates. The rate of days spent in hospital per month was 0.06 (95% CI, 0.03 to 0.10) while receiving IVIg and 0.02 (95% CI, 0.01 to 0.03) while receiving IgHy10. Whether the days spent in hospital per month include time spent in hospital was due to infusions is unknown. The monthly rate of days spent in hospital due to infection was 0.03 (95% CI, 0.01 to 0.05) while receiving IVIg and zero days/month while receiving treatment with IgHy10. No days spent in hospital is a treatment goal for patients with humoral immunodeficiency, and these results were considered a clinically meaningful result by the clinical experts consulted by CADTH. Overall, these results describing healthcare utilization and productivity suggest there was minimal disruption to the everyday life of patients, as the number of acute physician visits, days in hospital, and days in hospital due to infection occurred at less than one day per month per patient. Similar assessments conducted in the extension study yielded comparable results, but reported annually.

In Study 160603, the point estimate for days off school or work during treatment with IgHy10 (Epoch 2 after the ramp-up period) and treatment with IVIg (during Epoch 1) was less than 1 day per month, or approximately 0.28 days per month (95% CI, 0.20 to 0.37) and 0.23 days per month (95% CI, 0.15 to 0.34), respectively. This suggests that patients experienced minimal disruption during IgRT in the trial, based on days of missed work or school.

Harms Results

The overall rate of AEs while receiving IgHy10 was 13.40 per patient during Epoch 2 of Study 160603 and 19.75 per patient prior to the safety follow-up of extension Study 160902. For reference, exposure to IgHy10 in Study 160603 was a mean of 38 days (SD = 10) during the ramp-up period plus 368 days (SD = 104) following the ramp-up period. In Study 160902, patients were exposed to IgHy10 for a mean of 566 days (SD = 212). The rate of AEs was 4.45 per patient during treatment with IVIg in Study 160603, and 7.78 per patient during the safety follow-up with IVIg or SCIg without hyaluronidase during the extension study. The most frequently

reported AEs while on treatment with IgHy10 was infusion site pain, which occurred at a rate of 1.14 events per patient, as well as the following AEs that occurred at a rate of less than 1 event per patient: headache, sinusitis, upper respiratory tract infection, asthma, nausea, fatigue, myalgia, infusion site pruritus, and viral upper respiratory tract infection. During the safety extension study, Study 160902, the overall rate of AEs was 19.75 per patient while receiving IgHy10. The rate of local AEs was 2.62 per patient and the rate of systemic AEs was 17.13 per patient (including infections) or 12.71 per patient (excluding infections).

Additionally, AEs were reported by patients during Epoch 2 following the ramp-up period. Overall, 53.1% of patients reported a local AE. The most frequently reported local AEs were infusion site pain, infusion site discomfort, infusion site erythema, and infusion site pruritus. From the available safety evidence, it is unknown whether local AEs were specifically related to hyaluronidase or SCIg. The most frequently reported systemic AEs were headache (30% of patients), asthma (17%) nausea (15%), pyrexia (15%), fatigue (15%), and the following AEs were reported in less than 15% of patients: myalgia, vomiting, arthralgia, dizziness, and diarrhea. Additionally, a post-hoc integrated analysis of safety outcomes from Study 160603 and Study 160902 reported the overall rate of systemic AEs and local AEs (both excluding infections) by age group (< 18 and ≥ 18 years). Among adult patients (≥ 18 years), 1200 systemic AEs were reported, corresponding to a rate of 8.63 AEs per patient-year. For local AEs, a total of 429 AEs were reported among adult patients, corresponding to a rate of 3.08 AEs per patient-year.

A total of 2 deaths were reported between the pivotal and extension study, both occurred during Study 160902. The deaths were caused by toxicity to various agents (n = 1) and cardiac arrest (n = 1), neither were considered related to the study treatments. Serious AEs were infrequently reported, with a total of 22 patients that reported a SAE in Study 160603 and Study 160902. Two SAEs due to chronic obstructive pulmonary disease were reported, which were the only SAEs reported more than once.

The majority of notable harms identified in the systematic review protocol were captured in the standard reporting of safety results. While receiving IgHy10 in Study 160603, systemic effects included as notable harms occurred at a rate of less than 1 AE per patient as previously described where overall AEs are summarized. Infusion site pain was the most frequently occurring infusion-related AE (1.14 AEs per patient) and other infusion-related events occurred at a rate of less than 1 AE per patient. For local reactions, swelling/edema and contact dermatitis were reported at a rate of less than 1 AE per patient, as were infusion site hypersensitivity and thrombotic events. No cases of hypersensitivity, anaphylaxis, thrombocytopenia, acute kidney injury, or aseptic meningitis were reported for patients receiving IgHy10 during Epoch 2.

Critical Appraisal

The evidence informing safety and efficacy of IgHy10 is based on two single-group, open-label studies. Neither a historical control or concurrent comparator group were used and consequently, there was no control for potential confounding variables. Additionally, it is not possible to infer causality for reported outcomes assessed in the trials, such as the annual rate of infections, which lacks context or a reference point for evaluation. The single-group study design was also a particular issue in the assessment of safety, in addition to outcomes that were reported as a rate per patient or per infusion. While this may partly account for varying duration of treatment in each of the reported observation periods, the proportion of patients experiencing a particular AE is unknown, with the exception of commonly reported AEs during treatment with IgHy10 in Study 160603. Most of the outcomes of interest for this review, including the primary endpoint of the pivotal trial, were not expected to have been impacted by an open-label design; however, patient reported outcomes such as those related to HRQoL, tolerability and adherence, and safety outcomes, may have been impacted based on patient beliefs about IgHy10. Risk of attrition bias is a concern due to the overall discontinuation rate in Study 160603, where 21% of patients discontinued from study primarily due to patient request for withdrawal or adverse events. Further, 43% of patients between the age of 2 and less than 12 years (N = 14) in Study 160603 discontinued from study either due to a requested withdrawal (29%) or AE (14%). As a result, the reported study results are likely biased in favour of IgHy10 as the data analyzed is largely based on patients who did not discontinue from study. Although the selection of outcome measures reported in the studies were considered clinically relevant, the methods of analysis hindered the ability to meaningfully interpret the outcomes. Statistical testing was only used for the primary endpoint in Study 160603, therefore multiplicity was not an issue. Within group changes were generally not reported as results were analyzed as a rate or summarized using descriptive statistics.

The clinical experts consulted by CADTH did not have any concerns regarding the generalizability of the evidence to groups of patients excluded from the trials (such as pregnant females, patients with IgA deficiency, patients required to remain on prophylactic systemic antibacterial antibiotics, or patients with certain pre-existing conditions) or Canadian patient specifically, despite only one

Canadian study site being included. There were also no concerns regarding the generalizability to patients with secondary humoral immunodeficiency, patients who were IgRT-naïve, or patients with lower serum levels of IgG. Concomitant use of prophylactic antibacterial antibiotic use and pre-medications used prior to administration of IVIg or SCIg were avoided if possible during the studies, but their use is common in clinical practice. The clinical experts consulted for this review suggested that an at-home training/support system would be implemented to facilitate administration of IgHy10 at home but the level of supervision in the trials was more intensive that what would be used in clinical practice. Lastly, IgHy10 was not studied in patients with secondary humoral immunodeficiency despite a proposed indication and reimbursement request for this patient population. However, the clinical experts consulted by CADTH were comfortable with extrapolating evidence of efficacy from patients with primary humoral immunodeficiency to patients with secondary humoral immunodeficiency.

Indirect Evidence

Indirect evidence matching the inclusion and exclusion criteria of this review was not submitted by the sponsor or identified in the CADTH literature review.

Other Relevant Evidence

Sponsor-submitted study in adult patients switching from cSCIg to IgHy10 (NCT02881437)

Description of study

NCT02881437 was a phase IV, open-label, non-randomized, single group prospective study, which filled an important gap in the comparison of cSCIg to IgHy10. The primary objective was to examine the difference in IgG trough levels at steady state among adults (18 years or older) with PID requiring IgRT during cSCIg treatment (primarily once weekly) compared to steady state IgG trough levels after switching to IgHy10 administration every other week at equivalent doses. Among the 22 enrolled patients, median age was 45.0 (IQR = 32.0, 54.0) years and 68.2% were female.

The study began with a 1-week ramp-up period (subcutaneous IgHy10 provided at one-quarter of the usual monthly cSCIg dose) which started 1 week after the last cSCIg infusion prior to enrolment. Subcutaneous IgHy10 infusions then occurred biweekly at one-half of the initial monthly cSCIg dosage, with follow-up measurements at 3 and 6 months.

Results

The mean change in steady state IgG trough level when switching from cSCIg to IgHy10 was -0.30 g/L (SD = 1.54) after 3 months, and -0.29 g/L (SD = 1.35) after 6 months (n = 16). A total of 11/19 (57.9%) patients had at least 1 infection in the first 3 months of follow-up, and 8/17 (47.1%) between 3 and 6 months of follow-up. The mean change in the physical component summary of the SF-36 was -0.90 (SD = 4.37) from baseline to 3 months and -2.67 (SD = 5.17) from 3 to 6 months (n = 12); mean change in the mental component summary was -2.67 (SD = 5.17) from baseline to 3 months and 1.33 (SD = 5.13) from 3 to 6 months (n = 14).

A total of 21/22 (95.5%) patients reported at least 1 local AE and all reported at least 1 systemic AE between baseline and 3 months follow-up; 12/22 (66.7%) reported at least one local AE and 16/22 (88.9%) reported at least 1 systemic AE between 3 and 6 months follow-up. Commonly reported AEs were similar to those in the pivotal studies.

Critical Appraisal

There are several internal validity concerns that limit the certainty of conclusions that can be drawn. The primary concern is that there is no control group and confounders are unaccounted for, thus causal relationships cannot be established. Though the inclusion and exclusion criteria are clear, some details of the participant disposition are limited (i.e., number screened versus randomized). The open-label design is likely to have biased the subjective endpoints (direction unclear). There were large losses to follow-up (6/22, 37%) which reduces the reliability of the findings for HRQoL. Statistical analyses were not adjusted for multiplicity.

Despite some differences in setting (all of the study sites were in France) and a narrower eligible population than would be seen in clinical practice, the clinical experts consulted by CADTH did not express concern in generalizing the evidence to Canadian adult patients. Applicability of the findings to children is less clear. Exposure to study treatments appeared to match the product monograph; aside from the ramp-up phase (not described in the monograph). Outcomes were clinically relevant; though the clinical

experts indicated that they would not rely on IgG trough levels alone for clinical decision-making. The sample size and length of follow-up may have been inadequate to capture rare and/or long-term harms.

Sponsor-submitted study on the safety of IgHy10 in pregnant women and their infants (Registry Study 161301)

Description of study

Study 161301 was a registry study providing safety data on women ever treated with IgHy10 and their infants – a population excluded from the pivotal studies. All pregnant women ever treated with IgHy10 were eligible in 1 of 2 study arms: (1) continued IgHy10 during pregnancy ('IgHy10 Arm'), and (2) switched to another IgRT or alternative treatment ('Alternative Product Arm'). Nine mothers were enrolled; they had a median age of 34.0 years (IQR = 32.0, 36.0), were primarily non-Hispanic/Latino (8/9, 88.9%), and all were White/Caucasian. From the mothers, 7 infants were enrolled. Patients visited their physicians and were treated according to routine medical practice. Data on IgHy10 treatment was available for 6 (85.7%) mothers in the IgHy10 Arm. Among these, the median number of infusions was 4 (IQR = 1.5, 5.75), received on a 3- or 4-week interval.

Results

Among the 9 mothers, 4 (44.4%) reported at least 1 AE; 3 (42.9%) mothers in the IgHy10 Arm and 1 (50.0%) in the Alternative Product Arm. There were no local or immunologic AEs. One (11.1%) mother in the IgHy10 arm reported SAEs. There were no AEs leading to death or WDAEs. Four (44.4%) mothers (2 in each arm) were assessed for anti-rHuPH20 antibodies and all were negative (titer less than 160). Eight (88.9%) mothers provided data on pregnancy outcomes; all were live births and 1 in the IgHy10 arm was considered abnormal as it was a cesarean section.

Infants were born at median 38.0 (IQR = 37.0, 40.0) weeks of gestation; weight, length, and head circumference were normal for all. Two (40.0%) infants in the IgHy10 arm had congenital malformations. During follow-up, 6 infants (85.7%) experienced at least 1 AE; 5 (100%) in the IgHy10 Arm and 1 (50.0%) in the Alternative Product Arm. 2 (40.0%) infants in IgHy10 Arm experience a SAE. There were no AEs leading to death or WDAEs.

Critical Appraisal

There are several internal validity concerns that limit the certainty of conclusions that can be drawn. The primary concern is that there is no control group and confounders are unaccounted for, thus causal relationships cannot be established. There was no statistical hypothesis testing. Selection bias is possible, as very few (n = 9) mothers were enrolled and it is not clear whether women from various centres would differ systematically. As this is an open-label study, subjective endpoints may be biased; however, the direction of the bias is unclear. Most of the data were collected retrospectively, which may have negatively affected quality and completeness. In the IgHy10 arm, 29% of mothers were lost to follow-up, which may have biased AE data in favour of IgHy10.

Despite some differences in setting (all of the study sites were in Europe or the United States) and a narrower eligible population than would be seen in clinical practice, the clinical experts consulted by CADTH did not express concern in generalizing the evidence to Canadian patients. The dosage and administration of IgHy10 appear to align with Health Canada approved dosing, however pregnant women are not an indicated population in the product monograph. The harm outcomes seem to be clinically important, but no efficacy outcomes were collected. The sample size and length of follow-up were likely inadequate to capture rare and/or long-term AEs.

Post-Authorization Safety Studies and Patient Registry Study

Results from two Post-Authorization Safety Studies, Global PASS (NCT02593188) and EU PASS (EUPAS5812), and a Patient Registry Study, FIGARO (NCT03054181), were submitted by the sponsor as supportive evidence. Both the Global PASS (N = 264) and EU PASS (N = 106) were non-interventional, prospective, uncontrolled, open-label, multi-center, post-authorization safety studies that evaluated the long-term safety of IgHy10 under clinical routine conditions in US and Europe, respectively. The Global PASS study was conducted between 2015 and 2021 and enrolled patients with PID. The EU PASS Study was conducted between 2014 and 2021 and enrolled patients that were prescribed treatment for PID or SID. The Global PASS reported that 56% of 909 infusions were self-administered at home. The EU PASS reported the proportion of treatments that were administered at a clinical site and at home, by year since the first fSCIg treatment. During first, second, third, and after the third year, 91.2% (n = 83 patients,

909 infusions), 93.2% (n = 556 patients, 600 infusions), 93.2% (n = 28 patients, 237 infusions), and 85.2% (n = 12 patients, 54 infusions) of treatments were administered at home, respectively. FIGARO was a long-term observational study on the utilization and outcomes of IgHy10 under everyday clinical practice conditions. FIGARO was conducted in Europe between 2016 and 2021 and enrolled 156 patients with PID or SID. Data was available for 154 patients, of which 13 were pediatric (less than 18 years), 120 were adults (18 to 64 years), and 21 were older adults (at least 65 years); results were analyzed by patient age. FIGARO reported that 81.7% of adults and 57.1% of older adults infused at home.

The results provided by the sponsor for infusions administered at home in Global-PASS, EU-PASS, and FIGARO suggest that the ability to administer treatment at home was more successful in a real-world setting than the clinical trial setting. However, the generalizability of this evidence to patients treated in Canadian clinical practice is unknown. Additionally, the interpretation of the additional evidence should take in consideration the limitations associated with real world evidence studies.

Post-hoc analysis

A post-hoc analysis by Wasserman et al. (2021) of 3 studies, which included a subset of patients with primary immunodeficiency who participated in 3 consecutive, open-label, uncontrolled clinical studies of IgG therapy was submitted by the sponsor as supportive evidence. Two of the three studies were Study 160603 and 160902, which informed the systematic review of HyQvia performed by CADTH Clinical Report. The retrospective post-hoc analysis included 30 patients that received at least 1 infusion of each type of therapy, i.e. IVIg, cSCIg, and fSCIg, and was designed to evaluate the efficacy (rates of infection) and tolerability of the three routes of IgG administration. The duration of exposure, total number of infusions, and mean IgG dose received during a 4-week period differed between the three treatments. As noted in the publication, limitations of the study include a small sample size, selection bias as study participation was voluntary, and year to year variations in community infections and other factors that change over time, which cannot be accounted for in a sequential study design. The post-hoc analysis concluded that across the three treatment modalities (IVIg, cSCIg, and fSCIg), annualized rates of validated acute serious bacterial infections (0, 0.09 and 0.04, respectively) and all infections (4.17, 3.68 and 2.42, respectively) were similarly low.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult Canadian patients with primary immunodeficiency (PID) or secondary immunodeficiency (SID), aligned to the anticipated Health Canada indication.
Treatment	Human immunoglobulin and recombinant human hyaluronidase (IgHy10)
Submitted Price	$91.8751 per gram of IG, 10% Available as: • 2.5 g/25 mL and 200 units/1.25 mL; $229.69 • 5 g/50 mL and 400 units/2.5 mL; $459.37 • 10 g/100 mL and 800 units/5mL; $918.75 • 20 g/200 mL and 1600 units/10 mL; $1,837.50 • 30 g/300 mL and 2400 units/15 mL; $2,756.25
Treatment Cost	At the submitted price, the annual cost of IgHy10 is estimated to be $54,888 per patient with SID or PID
Comparators	IVIGs (mix of comparators including Gamunex, IGIVnex, Gammagard Liquid, Gammagard S/D, Octagam, Panzyga, and Privigen) SCIGs (mix of comparators including Cutaquig, Cuvitru, Hizentra, and Xembify)
Perspective	Canadian publicly funded health care payer
Time horizon	One year
Key data source	Study 160603 (pivotal study) and study 160902 (extension study): phase III, open-label, non-randomized, single-group studies
Costs considered	Drug acquisition costs, hospital costs, infusion supply costs and CBS service costs

Component	Description
Key limitations	• The assumption of similar clinical efficacy for IgHy10, IVIGs, and SCIGs, used to support the submission of a cost-minimization analysis, is highly uncertain. Clinical evidence available for IgHy10 was based on two single-group, non-randomized, open label studies. Neither study provided any comparative evidence on the efficacy and safety of IgHy10 with IVIGs and SCIGs, and therefore, the comparative efficacy and safety of IgHy10 to IVIGs and SCIGs is unknown. • The sponsor's analysis is based on an outdated pre-NOC indicated population. • Pricing of IVIG and SCIG comparators used in the CMA are highly uncertain and likely overestimated. • Market share distributions should not be used to aggregate and average costs of IVIG and SCIG comparators in a CMA. Further, these market share may not reflect the distribution of these treatments for the indicated populations. • Patients with PID and SID were assumed to have differing doses; further, the use of a lower dose for each IVIG and SCIG product did not align with the dose typically used in Canadian clinical practice, and likely underestimated drug cost calculations. • Training costs for IgHy10 were not incorporated as part of the cost-minimization analysis and likely underestimated relevant costs under the public healthcare payer perspective.

CADTH reanalysis results	• CADTH conducted reanalyses that included excluding pediatric PID and SID patients; changing the individual price of all IVIG and SCIG comparators to better reflect prices in the Canadian market; evaluating the incremental cost of individual IVIG and SCIG comparators (rather than weighted IVIG and SCIG drug classes); and revising dosing assumptions to reflect clinical experts' feedback.
	• Based on CADTH reanalyses:
	  ○ In patients with PID or SID, IgHy10 was associated with a per patient incremental cost ranging from $14,731 to $35,250 versus IVIG products, and a per patient incremental cost ranging from $16,061 to $22,821 versus SCIG products, over a one-year time horizon.
	  ○ In order for IgHy10 to be similar in price to the least expensive comparator for both PID and SID, a 73% price reduction for IgHy10 is needed.
	• CADTH was unable to address the uncertainty associated with the comparative efficacy and safety of IgHy10 with IVIGs and SCIGs. As such, a cost-minimization analysis is likely inappropriate to assess the cost-effectiveness of IgHy10, and the cost-effectiveness of IgHy10 is unknown.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor's submitted base case is based on an outdated pre-NOC indicated population; pricing of IVIG and SCIG comparators used in the BIA are highly uncertain and likely overestimated; there is substantial uncertainty related to the market share in the reference and new drug scenarios; the use of a lower dose for each IVIG and SCIG product for both PID and SID patients did not align with the doses typically used in Canadian clinical practice for both populations; several parameters used to derive the size of the population eligible for treatment with IgHy10 are uncertain, including the prevalence of PID, the proportion of patients treated with IGs, and the annual incidence of PID; the discontinuation rate was likely overestimated.

CADTH conducted reanalyses that included excluding pediatric patients with PID and SID; changing the individual prices of all IVIG and SCIG comparators to better reflect prices in the Canadian market; revising the market share estimates in the new drug scenario; assuming patients with PID and SID would receive an equal dose and revising the dose for each IVIG and SCIG product for PID and SID patients; and changing the discontinuation rate.

Although the sponsor suggested IgHy10 would be associated with a budget impact of $786,819 over the three-year time horizon, based on CADTH reanalyses, the budget impact of introducing IgHy10 would result in an estimated budget impact of $43,636,227 in Year 1, $62,188,520 in Year 2, and $80,037,821 in Year 3, for a total budget impact of $185,862,568 over the three-year time horizon.

Canadian Plasma-Related Product Expert Committee (CPEC) Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Irene Sadek, Dr. Andrew Shih, and Dr. Peter Zed.

Initial meeting Date: November 25, 2021

Regrets

Two expert committee members did not attend.

Conflicts of Interest

None

Reconsideration meeting Date: April 28, 2022

Regrets

None

Conflicts of Interest

None