FINAL REPORT

NOVEMBER 22, 2019

PRESENTED BY:

CANADIAN IMMUNODEFICIENCIES PATIENT ORGANIZATION

SCIG SHORTAGE REPORT

Background

Please read this organization's IG Transition Report, published November 2018, which outlines the results from Canadian Blood Services (CBS)' last RFP for Plasma Protein Products, and how the resulting product mix and the transition to new product affected the Primary Immunodeficiency (PI) patient population in Canada.

Transition

PPP Mix 2013-2018	Sizes	PPP Mix 2018-2021(23)	Sizes
Gamunex	2.5g, 5g, 10g, 20g	Gamunex	2.5g, 5g, 10g, 20g
IVIGnex	20g	IVIGnex	20g
Privigen	**2.5g, 5g,** 10g, 20g, **40g**	Privigen	10g, 20g
Gammaguard Liquid	5g, 10g	Gammaguard Liquid	**2.5g**, 5g, 10g, **20g, 30g**
Panzyga	2.5g, 5g, 10g, 20g, 30g		
Hizentra	1g, 2g, 4g, 10g		
		Cuvitru	1g, 2g, 4g, 8g

IG transition basics

With almost 3000 SCIG patients transitioning from Hizentra to Cuvitru, this is the largest SCIG transition globally in history, with potential savings to the health ministries of the provinces of up to $498 million over three years.

The transition to the new product mix began in early 2018, with the official start date of April 1, 2018. It should be noted that patient training resources were not available to all clinics at the official start date.

CIPO Involvement

CIPO was asked to be a representative on the PPP RFP committee, and we accepted. Due to confidentiality, we are unable to disclose any conversation held during those proceedings. CIPO did publicly state after the contracts were announced, on December 6th 2017 at a CBS open board meeting, that we were concerned with the sole supplier of the in-home therapy subcutaneous immune globulin (SCIG). And requested that CBS place a small amount on order with a secondary supplier. CIPO was not alone in this action. The CSACI, GBS/CIDP Foundation of Canada and CHAEN all requested a secondary supplier.

SCIG

In 2017, Canada saw SCIG usage increase by 25%. At the end of 2017 SCIG received a new indication for a neurological condition, CIDP, as well as a positive recommendation from the OHTAC. These two factors are part of the reason for the increase in SCIG usage, but not the only ones. With fewer side effects, SCIG has become the clinical standard over IVIG.

Shortage

On May 4th 2019, patient organizations, treating physicians, nurses and CBS were brought together in Toronto by Takeda Pharmaceuticals for a meeting on the transition. This was scheduled as an 18-

month follow-up to a meeting that had taken place in December 2017. The agenda had been set to look at the transition 1 year in from all perspectives. Attendees were asked to complete a pre-meeting survey about their experience with the transition to-date. At 10am, during Takeda's presentation on the transition from their perspective, the following was announced:

- There had been an unforeseen growth in the number of SCIG patients (50%) with 50-60 new patients per month
- Takeda had not planned for this growth
- If growth continued at this rate, Takeda could not supply product in 6 weeks

We were informed that Takeda did have enough Cuvitru for current patients, and that patients already on treatment would not be affected.

We were also informed that a letter had been drafted and would be going out to all blood banks the following week, containing the following:

Until further notice (Fall 2019):

1. No new SCIG patients
2. All new patients were to be started on IVIG
3. Current patients to pick up only 1 month of Cuvitru

Potential Issues

On the announcement of the impending shortage, and the drafted letter, several issues were highlighted.

- **Adverse Events/Reactions:** SCIG is regarded as the first method of choice due to the lower rate of adverse events and reactions compared to IVIG. IVIG is not deemed a practical option in many cases.
- **Clinical Capacity:** Many clinical IVIG programs have been capped or have long wait lists of up to 6 months, making IVIG not a viable alternative for patients awaiting treatment.
- **Patient Anxiety/Stress:** Limiting the amount of product pick-up for current patients can cause unnecessary stress and anxiety for patients. If patients are cautioned that their products are in danger, they are more likely to hoard or titrate their own product.
- **Treatment Access**: Allowing private industry to determine whether a treating physician can deny or allow access to a particular method of treatment to a patient raises an ethical question.

Other Issues

During the course of the SCIG shortage, other potential issues (some not within CIPO's remit) arose.

- **Communication**: Stakeholders (Treating physicians, nurses, patient organizations, blood banks) were not informed until the situation was at a crisis point and a plan was already in place, with letters drafted, by CBS and Takeda.
- **Planning**: CBS and Takeda did not foresee the supply challenges that were faced.
- **Administration constraints:** Blood banks and clinics face an administrative burden and increase in workload due to the shortage and supply challenges.
- **Data:** Not tracking the necessary data, and relying on industry to provide it, has proven to be problematic.

Solution - Focused

A working group was established representing patient groups, treating physicians from neurology and immunology and nurses. It was decided that they create recommendations to assist with the shortage.

The Working Group

In the spirit of transparency and to keep communication open, the Executive Directors of CIPO and the GBS/CIDP Foundation of Canada, along with their medical chairs, headed up the working advisory group on IG supply. Reaching out to the prominent treating physicians, in regards to SCIG in Canada, the group meet weekly via teleconference throughout the crisis.

The group set out their own recommendations to help curtail the use of SCIG during the crisis, which were sent to CBS and to the NEBMC for adoption. (APPENDIX A)

The group wrote to all pharmaceutical companies in Canada with a SCIG product on the market, asking them their plan to support patients and the future of IG in Canada.

CBS asked the working group to supply recommendations for the reintroduction for Cuvitru, when the supply was once again well established. The group did and the recommendations were once again adopted. (APPENDIX B)

CIPO and GBS/CIDP Foundation of Canada write joint letters to patients once a month which were posted on their website, social media and disseminated to all members.

Inclusion/Collaboration

CBS was invited to join the beginning of each call to update on the supply. After the first two weeks, the Chair and Vice-Chair of CBS' National Advisory Committee also join the working group, while two members of the working group were invited to join the NEBMC meetings for the duration of the crisis.

The Role of CBS

CBS claimed that there was no forecasting (including global) that could foresee the increase in SCIG usage. CBS assured the group that they were in discussions with the other vendors to source alternate product. They did secure an amount of both Hizentra and Cutaquig.

Alternate Product Sites

Two clinics (Edmonton and Ottawa) volunteered to transition their patients onto alternate SCIG products to help ease the supply strain on Cuvitru. CBS informed the working group that the alternate product would only be until the supply of Cuvitru was re-established, at which point those patients would transition back to Cuvitru. Working together, CBS, the clinics, private industry and the working group have facilitated that these patients remain on the alternate product long term.

End

On August 21, 2019 the NEBMC lifted the Amber alert for Cuvitru, putting into effect the recommendations set out by the working group for the re-introduction of Cuvitru.

IVIG Challenges

Due to the SCIG shortage, clinics and blood banks across Canada were having to substitute vial sizes. Perhaps because of this, we became aware of on July 4 shortage of certain vial sizes in Gammaguard

Liquid, the IVIG product. These shortages became more apparent as the months passed and on October 18 were informed of changes to the product mix by CBS. The IVIG supply challenges continue today.

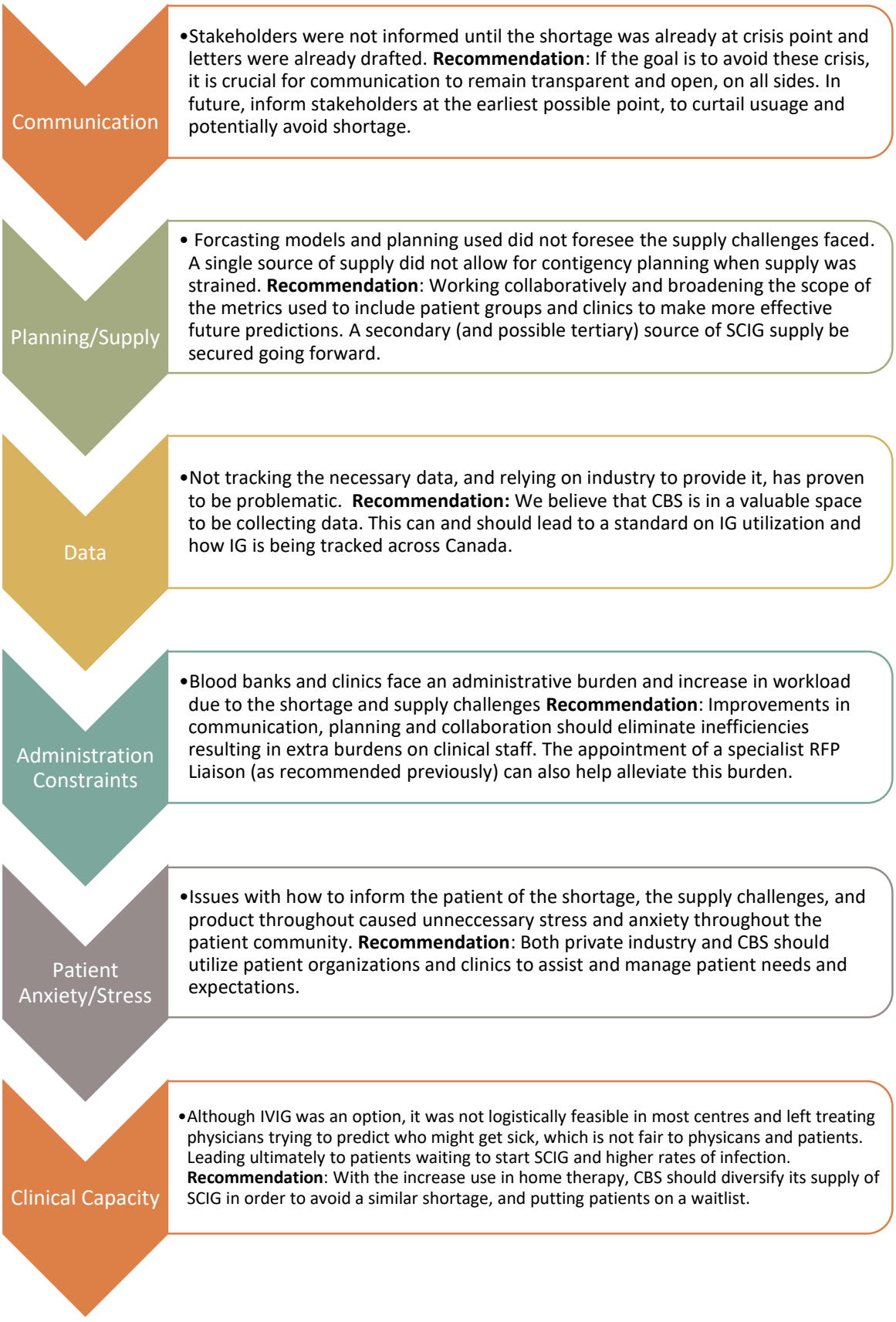
SCIG Shortage Timeline

Date	Event
05/04	Stakeholders informed of SCIG Shortage (6 weeks of supply)
05/10	Working Group on IG Supply informed 2.5 weeks supply
05/14	NEBMC issues Amber Alert
05/15	Working Group issues recommendations on SCIG use
05/15	CIPO & GBS/CIDP Foundation of Canada issue 1st Patient Letter
05/16	One Path issues letter to patients on program
06/06	Work Group issues letter to manufacturers of SCIG
06/13	CIPO & GBS/CIDP Foundation issue 2nd patient letter
07/04	Takeda issues letter to expect vial size substitutions in Gammaguard Liquid
07/09	Working Group issues recommendations on the reintroductions of Cuvitru
07/17	CBS issue letter regarding short supply of 5g, 10g, 30g Gammaguard Liquid (leaving only 2.5g and 20g vials available)
07/19	CIPO & GBS/CIDP issue 3rd patient letter
08/15	CIPO & GBS/CIDP issue 4th patient letter
08/21	NEBMC lifts SCIG advisory
09/05	CIPO & GBS/CIDP issue 5th and final patient letter
10/18	CBS issue Gammaguard Liquid supply constraint letter announcing changes to the overall product mix through March 2020

CHANGE MANAGEMENT PROCESS

POSSIBLE SOLUTIONS

CIPO has identified possible steps to resolve some of the issues which have arisen with the transition. Through collaborative efforts, we hope that our recommendations can work towards implementing a satisfactory resolution.


Communication
•Stakeholders were not informed until the shortage was already at crisis point and letters were already drafted. **Recommendation**: If the goal is to avoid these crisis, it is crucial for communication to remain transparent and open, on all sides. In future, inform stakeholders at the earliest possible point, to curtail usuage and potentially avoid shortage.
Planning/Supply
• Forcasting models and planning used did not foresee the supply challenges faced. A single source of supply did not allow for contigency planning when supply was strained. **Recommendation**: Working collaboratively and broadening the scope of the metrics used to include patient groups and clinics to make more effective future predictions. A secondary (and possible tertiary) source of SCIG supply be secured going forward.
Data
•Not tracking the necessary data, and relying on industry to provide it, has proven to be problematic. **Recommendation:** We believe that CBS is in a valuable space to be collecting data. This can and should lead to a standard on IG utilization and how IG is being tracked across Canada.
Administration Constraints
•Blood banks and clinics face an administrative burden and increase in workload due to the shortage and supply challenges **Recommendation**: Improvements in communication, planning and collaboration should eliminate inefficiencies resulting in extra burdens on clinical staff. The appointment of a specialist RFP Liaison (as recommended previously) can also help alleviate this burden.
Patient Anxiety/Stress
•Issues with how to inform the patient of the shortage, the supply challenges, and product throughout caused unneccessary stress and anxiety throughout the patient community. **Recommendation**: Both private industry and CBS should utilize patient organizations and clinics to assist and manage patient needs and expectations.
Clinical Capacity
•Although IVIG was an option, it was not logistically feasible in most centres and left treating physicians trying to predict who might get sick, which is not fair to physicans and patients. Leading ultimately to patients waiting to start SCIG and higher rates of infection. **Recommendation**: With the increase use in home therapy, CBS should diversify its supply of SCIG in order to avoid a similar shortage, and putting patients on a waitlist.

REVIEW FOR FUTURE SHORTAGES

RECOMMENDATIONS

The CIPO board, along with the CIPO Medical Science Advisory Committee, have reviewed these recommendations and found that if implemented in coordination and cooperation with interested stakeholders, industry, prescribing physicians, transfusion medicine and clinic staff, upcoming IG supply constraints will have less disruption and a significantly smaller impact on clinics, blood banks and patients.

CIPO looks forward to continuing to work with CBS to achieve the best possible outcomes for patients in Canada.

APPENDIX A:

WORKING GROUP RECOMMENDATIONS:

To Subcutaneous Immunoglobulin Prescribers and Blood Banks

Re: Cuvitru shortage

Canadian Subcutaneous Immunoglobulin (SCIg) prescribers were notified on Saturday 04-May-2019, at a meeting in Toronto, attended by representatives from Takeda Canada, & Canadian Blood Services (CBS), of an imminent shortage of Cuvitru brand SCIg in Canada. This affects predominantly patients with Immunodeficiency, receiving SCIg for replacement and patients with Neuromuscular Disease, receiving SCIg for Immunomodulation. We were told this shortage would interfere with the treatment of patients currently on SCIg if growth of SCIg use was not immediately curtailed. This was first announced on 29-Apr-2019 on Health Canada's website (https://www.drugshortagescanada.ca/shortage/82602). A Customer Letter from CBS and an explanatory letter from Takeda Canada can be found on the CBS website (https://blood.ca/en/hospital-services/customer-service/communications/customer-letters). CBS has assured us that they are working to find alternate sources of SCIg. Takeda stated that they hope to have sufficient product by "late-summer/early fall", most likely Sep-2019. Hema Quebec has an alternative supplier and is not affected.

As a result of the Cuvitru shortage, a working group consisting of Canadian neurologists, hematologists and immunologists who prescribe SCIg and patient advocates met by teleconference on 09-May-2019 to recommend short-term management to mitigate the risk to patients and their access to SCIg. We recommend the following strategy to SCIg treaters:

For Patients currently on SCIg with Cuvitru:

We recommend that currently treated patients continue with NO changes to their current access. Patients should be given no more than a 3 months' supply.

Given the limitation in access to larger vial sizes (4g and 8g), we recommend this supply should be preferentially available to neurology patients who require higher dosage.

For New patients not currently on SCIG

We recommend holding SCIg starts for patients who require SCIg except where SCIg is the only option deemed appropriate for that patient, (e.g. patients with urgent clinical need and poor venous access), until further notice and supply has been restored. We ask that treaters consult with and notify us if/when these situations arise. Supply of IVIg is not currently affected but there is limited capacity on outpatient units to treat patients with IVIg and patients should not be forced to start on IVIg if the preferred method is SCIg.

For assuring ongoing supply of SCIG:

We recommend that CBS work urgently to assure supply of SCIg through alternate suppliers. We recommend that CBS update the community on available supply and progress on obtaining alternate supply on a weekly basis

These recommendations aim to assure that the shortage of Cuvitru will have the least impact on patients currently receiving SCIg therapy while CBS works to obtain alternate supply.

CBS has agreed to provide regular updates to ensure all options to increase supply are explored as expeditiously as possible, including negotiating a supply of SCIg from alternate suppliers. Our recommendations are likely to change as more information becomes available. We will continue to advocate for all options in the best interest of our patients.

As information is made available it will be shared to all treaters as quickly as possible understanding that patients will depend on this information to receive the care they need.

Sincerely:

Stephen Betschel, Co-chair, Medical & Scientific Advisory Committee, Canadian Immunodeficiency Patient Organization (CIPO)

Whitney Goulstone, Executive Director, Canadian Immunodeficiency Patient Organization (CIPO)

Donna Hartlen, Executive Director, GBS/CIDP Foundation of Canada

Hans Katzberg, Medical & Scientific Advisory Committee, GBS/CIDP Foundation of Canada

Harold Kim, President of the Canadian Society of Allergy & Clinical Immunology (CSACI)

Bruce Ritchie, Co-chair, Medical & Scientific Advisory Committee, Canadian Immunodeficiency Patient Organization (CIPO)

On behalf of: Dr. Juthaporn Cowan, the Ottawa Hospital; Dr. Gina Lacuesta, Halifax; Dr. Steven Baker, McMaster University; Dr. Susan Waserman, McMaster University; Dr. Zaeem Sadiqqi, University of Alberta; Dr. Chrystina Kalicinsky, Winnipeg Health Sciences; Noor Nongfei Zhu, Fraser Health; Richard Thompson, Immunodeficiency Canada

APPENDIX B:

WORKING GROUP RECOMMENDATIONS: THE REINTRODUCTION OF CUVITRU

CIPO
Canadian Immunodeficiencies Patient Organization

GBS/CIDP
Foundation of Canada

CANADIAN SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY
SOCIÉTÉ CANADIENNE D'ALLERGIE ET D'IMMUNOLOGIE CLINIQUE
P.O. Box 51045, Orleans, ON K1E 3W4
613 986 5869

Recommendations for the re-introduction of Cuvitru for patients requiring subcutaneous immunoglobulin for the first time (new starts).

The supply of Cuvitru is improving but not all patients requiring SCIG can yet be started. The recommendations are meant to allow for a graded reintroduction of new starts to try to prevent additional shortages.

These recommendations are not meant to replace clinical judgement and may not apply to all clinical situations.

We would recommend that patients who urgently require immunoglobulin therapy and are deemed candidates for SCIG that priority be given to those patients who cannot receive IVIG. Reasons that patients may be deemed unable to receive IVIG include any or all of the following:

1) Intravenous access is not possible or would require unnecessarily invasive means to achieve IV access.

2) The patient has had significant adverse reactions with IVIG products despite premedication.

3) Administration of IVIG is not feasible for a given site due to significant lack of resources such as nursing or clinic capacity.

These recommendations are not meant to replace clinical judgement and may not apply to all clinical situations.

Working Advisory Group on IG Supply

Dr. Stephen Betschel, Co-Chair, Medical Science Advisory Committee, Canadian Immunodeficiencies Patient Organization

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