Canadian Hemophilia Society
Help Stop the Bleeding

February 25, 2019

Dear members of the bleeding disorder community,

The Canadian Hemophilia Society (CHS) objects to the recent Canadian Blood Services (CBS) decision to force children under 12 to switch away from Eloctate (rFVIIIFc).

The CHS Board of Directors took this position at its February 24 meeting, and called on CBS to reverse its decision.

The only exceptions to CBS' directive are those children who meet special access criteria such as being on a regimen for immune tolerance induction or being under the limit of 100 exposure days to factor VIII.

Following the most recent tender (called an RFP) for the period April 1, 2018, to March 31, 2020, CBS had agreed to continue to distribute extended half-life factor VIII Eloctate to children under 12 until a second extended half-life factor VIII, Adynovate, was granted an indication for this age group. Health Canada approved Adynovate for children under 12 in November 2018. Many observers had expected Health Canada to await more robust safety data. In early February 2019, CBS wrote to Canadian bleeding disorder treatment centres and said:

> *With the Health Canada approval of Adynovate® for pediatric patients, patients less than 12 years of age currently receiving Eloctate® who have not been approved under any of the other exceptional access criteria are now required to transition to another factor VIII product. Canadian Blood Services provides a broad choice in factor VIII product selections with Adynovate®, Kovaltry®, Nuwiq® and Xyntha® available.*

A chart developed by the CHS describing all FVIII concentrates approved and/or available in Canada can be found on its website at: **www.hemophilia.ca/wp-content/uploads/2018/11/rFVIII-Chart-29-11-2018.pdf**.

To the best of our understanding, families will be forced to use alternative products the next time they need to replenish their home infusion inventory.

While the CHS understands that Adynovate is considered to also be an extended half-life FVIII, that extension is achieved through PEGylation (PEG). PEGylation is the process of attaching polyethylene glycol polymer chains to molecules and macrostructures, such as a therapeutic protein like factor VIII.

While the risks related to PEGylation of FVIII remain theoretical, physician and caregiver concerns are real. The European Medicines Agency has withheld the indication for children under 12 years. It writes in its 2017 Assessment Report:

> *… there remain uncertainties in relation to whether the younger children would be more vulnerable for potential PEG induced effects, including cell vacuolation, than adults. Due to the lack of a well-designed toxicology study of at least 3-month duration with the PEG molecule used in Adynovi® (or a relevant surrogate) and appropriate data to support safe use in children, the use of Adynovi below the age of 12 is not supported from a nonclinical perspective.*

The CHS can certainly understand the many parents who have told us they do not want to impose this risk on a young child if there is an alternative.

Note that none of the regulatory agencies—Health Canada, the United States' Food and Drug Administration and the European Medicines Agency—have expressed any concerns about PEGylated products in people 12 years of age and older.

The CHS appreciates that there are three other high-quality standard half-life factor VIII concentrates distributed by CBS to which patients could switch. Switching to them, however, would likely mean 52 extra infusions per year in young patients on prophylaxis for whom venous access is extremely challenging.

A recent analysis by Dr. Alfonso Iorio from the Hamilton Health Sciences Centre of seven studies comparing standard half-life FVIII with extended half-life FVIII demonstrated a significantly lower annual bleed rate with extended half-life FVIII.

The CHS has made every effort to support the CBS decisions resulting from RFPs over the last many years. This one, however, we cannot support. We are informing you, our community, of our position and the reasons for it.

The CHS encourages families affected by this forced switch to discuss their options with their treating physicians.

If not satisfied with the prospect of switching, please communicate your concerns to Canadian Blood Services (feedback@blood.ca) or 1-888-236-6283.

In addition, we invite you to let the CHS know how you feel about this forced switch (chs@hemophilia.ca). If you would like further information on the CBS directive and decision of the CHS Board of Directors and the literature that supported it, please contact us. Watch the CHS website (www.hemophilia.ca) for updates.

Sincerely,

Paul Wilton, President, Canadian Hemophilia Society