Canadian Blood Services Therapeutic Blood Product Review Process

**Corifact™**

The National Advisory Committee on Blood and Blood Products (NAC) was asked and agreed to participate in the Canadian Blood Services Therapeutic Drug Product Review Process for Corifact™.

The NAC member that actively participated in this step of the review process and subsequently provided individual answers to the questions posed by Canadian Blood Services is:

**Dr. Jennifer Fesser (PEI)**

**Queen Elizabeth Hospital**

**Charlottetown PEI**

The individual review (attached) was forwarded to the NAC membership for feedback and additional commentary. Overall, the NAC members representing the provinces agree with the review as it is written and it adequately reflects the view of the membership:

**Response tabulation (including reviewer)**

Agreement = 8 (includes 2 CBS medical reps)

Disagreement = 0

Responses not received from members were due to their unavailability at the time the review was circulated.

There were no disclosures received from members indicating any dealings with CSL Behring that our organization currently have or have had within the last 24 months.

**Member comments:**

Your review appears all encompassing. I have nothing further to suggest.

I agree with Jennifer’s very excellent review and decision document.

I reviewed Jennifer’s paper - very well done. Nothing to add at this time.

I’ve read the review that Dr. Fesser wrote and fully support the conclusions.
I agree with your review completely. I also had a quick theoretical chat (if you had Tretten and Corifact in your hands, would you choose one over the other and why) with our Hemophilia Treatment Centre. It looks like the treaters view them as equivalent save for the subunit issue. Patients are not going to be switched until mutation has been identified and this is a slow process because there is only one place in Canada that does it. Having said that, these patients are so rare that genotyping them is not an insurmountable task. There is also this old sentiment which is very true and strong in this patient population: if the old product is working for you, why change.

Having said that, possible reasons for switching would be 1) volume to be infused - if different; smaller volume may be preferable; 2) ease of reconstitution and administration - if different; more user friendly product will of course be more preferable 3) Jehovah Witness patient - who may not want any human or animal blood proteins in the product - which Tretten of course is free of those.

This was an excellent and well referenced review Jennifer - thanks! One question - do you feel NAC should recommend a companion framework document with respect to the dosing or wait for the CBS PT BLC to direct us after they read all of the stakeholder feedback?

Note: Regarding the above question: The NAC, Chair determined to await direction from CBS/PT if such a document on dosing is determined to be required.

_The NAC formally supports the availability and distribution of Corifact™ by Canadian Blood Services._
Therapeutic Drug Product Review Process for Corifact™ completed by Dr. Jennifer Fesser.

Further information

The factor XIII enzyme is composed of two A-subunits and two B-subunits linked by noncovalent bonds, and has a half-life of approximately 9-14 days. Congenital factor XIII deficiency is a rare condition which may cause moderate to severe bleeding, recurrent abortions, and impaired wound healing. The incidence of severe Factor XIII deficiency is estimated at 1 in 3-5 million, with >95% of cases attributable to abnormalities of the A-subunit. The main cause of death / disability in congenital Factor XIII deficiency is intracranial hemorrhage, which has an incidence of 25-30%, and prophylaxis with Factor XIII concentrates / cryoprecipitate is generally recommended.

CSL Behring’s (CSLB’s) Factor XIII Concentrate (Human) is a heat-treated plasma-derived Factor XIII replacement that is presently licensed in 13 countries and has been marketed since 1993. It requires refrigerated storage, and may be kept for up to 36 months. It is tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV, and by Nucleic Acid Testing (NAT) for HCV, HIV-1, HAV, HBV and Human Parvovirus B19. Finally, the product is heat treated (+60°C for 10 hours in an aqueous solution) and virus-reduced by filtration two 20 nm filters in series.
Question 1

Give a brief commentary on the publications included in the submission that you believe are the most pertinent for Canadian Blood Services’ evaluation of this product.

The 261 studies included for review fall into 3 basic categories:

1) older studies (starting from the 1990s) performed by the manufacturer to establish the pharmacokinetics of plasma-derived heat-treated Factor XIII. Overall, the pharmacokinetics studies included relatively few patients, are relatively short in duration and use relatively high doses of Factor XIII (40 U/kg every 28 days).

2) more recent studies (2000s) looking at the clinical effectiveness of the product

3) technical or historical papers (clinical descriptions of the disorder and early treatment interventions, other uses of Factor XIII, non-human research studies)

The most relevant studies include BI71023_3001A (data published by Nugent in 2012), a phase 3b study by the manufacturer of the safety and efficacy of the heat-treated plasma-derived Factor XIII. It was conducted over twelve months between 2009 and 2011, and included 41 subjects receiving 40 U/kg every 28 days. Five mild to moderate spontaneous bleeds, all with predisposing factors, were reported, but none required treatment with Factor XIII. Treatment with Factor XIII ameliorated bleeding in study subjects who underwent surgery. No serious adverse events attributable to the product were reported, even in a patient who received more than a 3 fold overdose. No thrombotic events, viral infections or development of anti-Factor XIII antibodies occurred. A subsequent manufacturer’s study (BI71023_3002) generated similar conclusions. Independent investigators (Dreyfus et al in 2011) looked at 19 patients receiving either prophylaxis or on-demand therapy with Fibrogammin P, and concluded that prophylaxis decreased the number of bleeds, and that Fibrogammin P provided good or excellent control of hemorrhage. No serious adverse events (including thrombotic episodes) occurred.

These studies support the clinical experience over the last two decades which has found Factor XIII to be a generally safe and efficacious treatment of congenital Factor XIII deficiency.
Question 2

Are you aware of any other publications that should be considered? Please specify.

No.

Question 3

Please identify any issues or concerns with respect to Corifact that should be considered by Canadian Blood Services with respect to:

A) Indication or efficacy
B) Safety
C) Storage
D) Administration
E) Product and/or package labeling

The manufacturing process, composition, and product package of Corifact 250/Corifact 1250 is identical to Fibrogammin-P (250 and 1250), other than for the fact that Corifact will be produced only from US sourced plasma. Despite the fact that the two products are essentially identical, the indications for Corifact are more restrictive; however, this is unlikely to be significant since prophylactic use of the product in patients to prevent intracranial hemorrhage would likely also address other concerns (e.g. pregnancy loss\(^1\)). Of more concern the fact that the recommended dosing of Corifact is 40 IU/kg bodyweight every 28 days (4 weeks), whereas the dosage for Fibrogammin is in the range of 10-35 IU/kg bodyweight approximately once a month; expert opinion based on clinical experience recommends 10 U/kg\(^2\). As such, it would be prudent to introduce expert consensus dosing guidelines along with the product.


Question 4

Are there specific advantages or disadvantages that Corifact has versus Tretten considering the respective licensed indications.

With respect to the licensed indications, Corifact has three advantages. First, it is licensed to treat those very rare individuals who have B-subunit deficiency, whereas Tretten is only licensed for use in those with A-subunit deficiency. This is not expected to be a large effect since congenital Factor XIII deficiency is extremely rare, and most individuals have A-subunit deficiency. Second, Tretten is not licensed for treatment of bleeding (only prophylaxis), presumably due to the absence of published data to support its effectiveness for this indication, whereas Corifact is licensed for perioperative management of surgical bleeding. Third, while the safety of Corifact (in the form of Fibrogammin P) for pregnant women and children has been established, there is no literature on the safety of Tretten in pregnant women and children <6 years of age. Beyond the licensed indications, Tretten has an advantage in that it is recombinant and does not contain any human / mammalian proteins. It is important to also note the price differential between Tretten ($10.82 / IU) and Corifact (projected to be $1.40 USD / IU).

Question 5

Would you be more willing to treat your patients with Corifact in place of Tretten, less willing, or indifferent? Please provide rationale. Would you be willing to switch patients from one product to another?

Given the broader clinical experience with and excellent safety history of Fibrogammin P, the wider range of licensed indications of Corifact and the more reasonable pricing of Corifact, I would be comfortable treating patients with Corifact in place of Tretten, and would be willing to switch patients from Tretten to Corifact as clinically appropriate.

Question 6

Corifact is only licensed for treatment of patients with congenital Factor XIII deficiency. Are there any other therapeutic indications for which you believe this product could be used? Please provide rationale / references.

Although there are scattered case reports of Factor XIII use in the treatment of various acquired Factor XIII deficient states, there is no evidence from controlled trials and no consensus on the appropriate treatment of acquired FXIII deficiency patients³.

Question 7

Specifically what do you believe is the role, if any, of Corifact in treating patients with congenital factor XIII deficiency versus other treatment options?

Corifact is preferable to fibrinogen for the treatment of congenital Factor XIII deficiency, owing to its superior safety profile. Owing to a lack of safety data, Corifact is preferable to Tretten for the treatment of patients with B-subunit or unknown type deficiency, pregnant females and children less than six years of age. Given the paucity of data on Tretten, Corifact would be the only licensed treatment for bleeds in congenitally Factor XIII deficient patients. Given the numerous circumstances were Corifact is preferable, and the substantial price differential, Corifact has a major role in treating patients with congenital Factor XIII deficiency.

Question 8

Is the manufacturer recommended dosing for Corifact clinically applicable? If yes, please provide rationale. If no, please provide clinically relevant dosing recommendations and references as applicable to all therapeutic indications for which you believe this product could be used.

The dosage of Factor XIII recommended by clinical experts for prophylaxis is 10 U/kg. The recommended dosage of Fibrogammin P (as licensed in the UK) is 10 IU/kg for prophylaxis, 10-20 IU/kg for treatment of bleeds, and 10-35 IU/kg before surgical procedures. Given that Fibrogammin P and Corifact are functionally identical products, there is no rationale to support the recommended dose of 40 IU/kg for prophylaxis. In fact, in the manufacturer’s own study (BB-IND-5986) is it noted that “based on previous reports, a generally accepted dosage range for prophylaxis in patients with Factor XIII deficiency is 10 to 20 U/kg every 4 to 6 weeks”.

Question 9

Based on its clinical effectiveness and safety profile, is this a product that should be carried by Canadian Blood Services? Yes or No, and why? If yes, for which indications?

Given the extensive experience with Fibrogammin P, Corifact is a product that should be carried by CBS for prophylaxis and treatment of bleeding in congenitally Factor XIII deficient patients. Corifact is, by virtue of its specificity and pathogen inactivation manufacturing processes, a superior product to the use of cryoprecipitate, and demonstrates more versatility in terms of patient population and indications than Tretten.

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