ascia
australasian society of clinical immunology and allergy

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Michael Stone
Deputy Chief Executive
Commercial Blood products and Business Services
National Blood Authority NBA

Dear Michael,

On behalf of the Australasian Society of Clinical Immunology and Allergy (ASCIA) I am providing a response to your questions regarding additional products for the management of Hereditary Angioedema (HAE) from CSL Behring. I have addressed the items you have outlined in the narrative that follows.

1. **Berinert 1500IU intravenous.**
   Currently Berinert intravenous is available via the NBA for Hereditary Angioedema(HAE) patients who fulfill requirements for access, for acute treatment, short term prophylaxis and for long term prophylaxis in those patients having eight or more HAE attacks per month. Dosage of Berinert intravenous is 20 IU/Kg, therefore for a 75 kg person the dose would be 1500IU or, with currently available supplies, 3x 500IU vials. The packaging is bulky and inconvenient for travel so having the one larger vial is an advantage. A number of patients receive 2000IU twice weekly so the larger vial availability is advantageous for them as it reduces the number of vials and packaging. Similarly, for those who carry Berinert for acute attack management, having the larger vial reduces bulk and drawing up from multiple vials.

   Providing doses are managed correctly, there should be no wastage-doses will be rounded up or down so that complete vials are used..

2.0 Berinert 2000IU and Berinert 3000IU subcutaneous.

These products are indicated for prophylaxis and in the clinical trials two doses were studied- 40IU/Kg and 60IU/Kg twice weekly. Both doses were efficacious but all results were better with 60IU/Kg resulting in the FDA stating that this is the recommended dose. To address the questions posed in “Attachment A” I provide the following information.

2.1 The need for prophylactic therapy

HAE is characterised by unpredictable attacks of swelling affecting the cutaneous and submucosal tissues. Some patients can identify triggers for swelling but other s experience completely random attacks. All HAE patients live with the possibility of a laryngeal attack that can be fatal without adequate and prompt treatment. While our patients have access to effective “on demand” therapy for managing acute attacks, this does not remove the anxiety and burden of living with uncertainty about when the next attack may develop. This limits petients’ ability to plan and take on various roles at work or in other aspects of life. As such, many studies have shown a poor quality of life in patients with HAE and a rate of anxiety and depression significantly greater than that of the general population. Prophylactic therapy addresses many of these issues in that attack rates reduce

substantially and patients can feel confident that attacks will not limit their activities. There is a general sense of well being that accompanies the removal of the threat of an attack.

For patients who live in rural and regional centres, there is inevitable delay in accessing acute treatments beyond what they may have at home so they have a compelling reason to minimise attacks. For other patients, there are certain life events that may exacerbate attack rates and disadvantage them at crucial times in their lives. Examples of this include big exams such as the HSC, important job interviews and so on.
The standard of care for patients with HAE must be good control of HAE attacks and that implies ***no attacks affecting an individual's quality of life.***

2.2 Available prophylactic therapies

Currently in Australia there are limited options available for management of patients with a high burden of disease from HAE. Traditionally tranexamic acid and danazol have been used. Tranexamic acid is relatively ineffective although a small number of patients find it useful. Its use is confined predominantly to paediatric practice where danazol is contraindicated. Danazol is still used with strong advice to maintain dosing to $\leq$ 200mg daily to minimise side effects that are particularly prevalent in female patients but occur also in male patients. However, efficacy of danazol is dose-dependent so the trade off between dosing for efficacy and minimising side effects results in many breakthrough attacks for the majority of patients managed in this way.

More modern and targeted therapies are available however access is very difficult. Currently the only funded effective therapy with minimal side effects is Berinert IV but it use is reserved for those who have eight or more HAE attacks per month – this is a huge disease burden and many patients have very poor quality of life with far fewer attacks.

Both lanadelumab (an anti-kallikrein monoclonal antibody) and Berinert SC are registered in Australia however neither are funded so access is impossible at the present time. Both these modern treatments are available to patients in USA and in some countries in Europe.

2.3. Criteria for prophylaxis eligibility

Criteria proposed for prophylaxis in HAE patients have changed and evolved over the last 16 years since the first attempt was made to define criteria.

In 2003 both the Canadian consensus guidelines and the Hungarian HAE Workshop proposed that patients with at least 1 attack or severe event per month or 5 days or more of disability per month would be candidates for long-term prophylaxis therapy.

In 2005 the UK guidelines added: Patients who do not sufficiently respond or do not have access to on-demand treatment may also be candidates for long-term prophylaxis therapy.

In 2011 the Canadian guideline revision *(Bowen T. Hereditary angioedema: beyond international consensus. Allergy Asthma Clin Immunol. 2011;7:1)* mandated an individualised approach stating that thresholds of number of attacks per month or days of disability are arbitrary and patients should not be required to have failed androgen therapy to be candidates for prophylaxis with C1-INH therapy.Using haemophilia and immunodeficiency treatment models for HAE the goal of treatment is to normalise a patient's life not merely treat individual bleeding or infection events taking into account costs and evidence of benefits and risks.

In 2012 three major international consensus statements were published.
(*Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor defi- ciency: consensus report of an International Working Group. Allergy. 2012;67:147–157.Craig T, Aygoren-Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. World Allergy Organ J. 2012;5:182–199).*

All advocated for individualised treatment with the goal of normalising quality of life;
long-term prophylaxis is appropriate for patients who are inadequately treated by on-demand therapies. Consideration for prophylaxis should take into account multiple factors, such as the severity of disease, frequency of attacks, patient's quality of life, availability of resources, and failure to achieve adequate control by appropriate on-demand therapy.

This is the position that ASCIA HAE working party has adopted as being "best practice" and this will be incorporated into the revision of the ASCIA document.

2.3. Uptake of Berinert SC in Australia

At the present time, only Berinert IV is available under very restrictive criteria, for HAE prophylaxis. It is likely that the majority of the present treated population will transition from IV therapy to Berinert SC when it becomes available**.** While many patients have learnt self-cannulation it can be difficult and there is always the risk of bleeding and infection. More importantly, after time, there is scarring and fibrosis and cannulation becomes difficult. There are compelling reasons to avoid insertions of portacaths in patients with HAE as there are instances of clotting and embolus formation as complications in this patient group.

There are patients currently receiving Berinert IV who are still not well-controlled. The data suggests that Berinert SC will be more efficacious for this subgroup as levels are higher and more stable. (see published evidence below).

Therefore, if the present criterion of requiring eight or more attacks per month is kept, then I would envisage most, but not all, patients receiving Berinert IV at the present time will transition to Berinert SC. Some patients are very well controlled on the IV treatment and have no difficulty with cannulation and may choose not to risk change. A small increase in uptake of Berinert SC prophylaxis may be expected as a number of patients who qualify with these criteria are precluded from prophylaxis with Berinert at the present time because IV access is impossible – this applies to some very obese patients and to some children. An informal poll of several Immunologists who treat HAE patients revealed that there may be 10%-20% increase in patients receiving prophylaxis over the present situation and with the present criteria in place.

As a treating physician, I have the expectation that criteria for offering prophylactic therapy in Australia will be reviewed and will be brought in line with international standards so a wider range of patients may access this life-changing treatment. Factors to be considered between a patient and the treating physician would include impact of attacks and the threat of attacks on life and daily living; access to acute treatment and medical facilities; debility caused by attacks, particularly abdominal and genital attacks; occurrence of laryngeal attacks; other psychosocial factors.

2.4 Evidence of benefit from Berinert SC prophylaxis

A summary of two important publications is outlined below:
Results from longterm study with Berinert sc prophylaxis (JACI In practice 2019)

- C1-INH(SC) was well tolerated and adverse events were infrequent and generally mild to moderate.

- No neutralising antibodies to C1-INH were reported.
- The median annualised attack rate was reduced to 1.0 attack per year.
- 86% of patients in the 60 IU/kg group achieved an attack rate of <1 attack per month.
- Most HAE attacks were mild to moderate and there was a trend to further improvement over time on prophylaxis.
- 23 patients receiving 60 IU/kg for >2 years, 19 (83%) were attack-free and 20 (87%) did not use any rescue medications during months 25 to 30 of treatment
- Rescue medication use was very low: 62% of patients did not use any rescue medication within 1 year in the 60 IU/kg treatment arm.
- Consistent with the placebo-controlled COMPACT trial, the approved 60 IU/kg dose shows a numerically better prophylactic effect than 40 IU/kg.

Efficacy of Berinert SC compared to Berinert IV for prophylaxis*(Craig T et al. Treatment Effect of Switching from Intravenous to Subcutaneous C1-inhibitor for Prevention of Hereditary Angioedema Attacks: COMPACT Subgroup Findings. JACI In Practice 2019)*
In the absence of prospective head-to-head comparisons of C1-INH(IV) and C1-INH(SC), this post hoc analysis:

- Provides evidence of relative effectiveness of C1-INH(SC) compared with C1-INH(IV)
- Suggests that patients on C1-INH(IV) prophylaxis may experience a clinically meaningful reduction of HAE attacks after switching to C1-INH(SC).

On average, attack rates during C1-INH(SC) use were reduced by about half (52%) compared with pre-study C1-INH(IV) prophylaxis; the median reduction of attacks per month was 74%.
C1-INH SC provides smoother and more steady levels over time that explains the increased efficacy.

2.5 Berinert SC **is not indicated** for on demand treatment. It takes approximately two weeks to reach a steady state. Berinert IV will continue to be required for on demand treatment for management of acute attacks in those where icatibant is ineffective or contra indicated and it will continue to be required for short term prophylaxis to cover for surgical and dental procedures.

3.0. Questions – Attachment A

1. Addressed on paragraphs 1 and 2 above.

2.*What are the implications of the proposed product improvements for clinical practice in Australia?*
Access to Berinert SC will lead to significantly better attack control with resultant improvement in patients' wellbeing and ability to function. Subcutaneous injection is far easier to manage, with fewer complications and greater safety over intravenous administration. It will enable those excluded from IV treatment to receive benefit.

3.*What is the prophylaxis regimen for intravenous access currently in Australia?*
Discussed in 2.2 above. Berinert IV use in AUstralia is reserved for those who have eight or more HAE attacks per month.

4. Addressed in paragraph 1.

5. *Are there potential risks associated with transition of patients from the current 500IU regimen?*
No. It is equivalent therapy,dosed per Kg, only with greater convenience and less packaging.

6. *Are there product specific factors or characteristics which support the clinical acceptability of Berinert SC for on-demand use?*

This treatment is NOT for on-demand use but purely for prophylaxis – it takes 2-3 weeks to reach a steady state. There is still an absolute requirement fo rBerinert IV fo rth eacute treatment.

7. Discussed in 2.3 above.

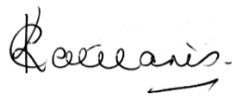
8.*What would be the likely prophylaxis regimen for subcutaneous use?*
While the trial data showed that a dose of 60IU/Kg was the most efficacious in clinical trial and this is the recommended dose in the USA, many patients received excellent benefit on 40 IU/Kg and only a minority had to step up to the higher dose to gain benefit. I would propose that it is acceptable to commence at 40IU/Kg **providing the physician has the ability to step up to the higher dose if attacks are not controlled after 2-3 weeks** when steady state is reached.

9.*Would current ASCIA clinical guidelines change based on availability of Berinert SC?*
Yes. In line with international guidelines, ASCIA would adopt a recommendation that Berinert SC is the preferred choice for HAE prophylaxis.

10. *Is there any other relevant information from a clinical or patient care perspective?*
HAE is an inherited, genetic disorder akin to other primary immunodeficiences and other rare enzyme deficiency disorders. The same criteria we apply to those disorders should an d must apply to HAE-replacement of the deficient factor to restore normal function so the patient's life is without the consequences of the deficiency.

I trust that these comments are useful in considering the NBA position regarding provision of effective prophylactic therapy for patients with HAE.

Yours sincerely,



CH Katelaris AM

Professor, Immunology & Allergy
Western Sydney University

Head of Unit, Immunology &Allergy
Campbelltown Hospital NSW

Chair, ASCIA HAE Working Party