National Blood Authority

Executive Summary

C1-Esterase Inhibitor Concentrate Utilisation Review

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Submitted to:
Research and Product Review
National Blood Authority

Submitted by:
Abt Associates
Level 2, 5 Gardner Close
Milton, Brisbane QLD, 4064

Acronyms and Abbreviations

Abt	Abt Associates
ACT	Australian Capital Territory
AHP	Approved Health Provider
C1-INH	C1-Esterase Inhibitor
ASCIA	Australasian Society of Clinical Immunology and Allergy
HAE	Hereditary Angioedema
IU	International Units
IV	Intravenous
LTP	Long Term Prophylaxis
MSAC	Medical Services Advisory Committee
NBA	National Blood Authority
NPPL	National Product Price List
NSP&B	National Supply Plan and Budget
NSW	New South Wales
NT	Northern Territory
PBS	Pharmaceutical Benefits Scheme
Qld	Queensland
QoL	Quality of Life
SA	South Australia
SC	Sub-cutaneous
TAS	Tasmania
Vic	Victoria
WA	Western Australia

Executive Summary

Background

The National Blood Authority (NBA) was established in 2003 and is a statutory agency within the Australian Government Department of Health and Aged Care portfolio. The NBA manages and coordinates arrangements for the supply of blood and blood products and services, including the provision of Berinert® intravenous (IV) and subcutaneous (SC), both C1-esterase inhibitor concentrates (C1-INH) used for the treatment of hereditary angioedema (HAE). These NBA funded C1-INH products are provided at no cost to patients through the national blood arrangements.

There are eligibility criterion associated with accessing NBA funded C1-INH that are included within the Australian Society of Clinical Immunology and Allergy (ASCIA) HAE Management Plan. The eligibility criteria for funded access were agreed by Australian governments, based on an assessment by the Medical Services Advisory Committee (MSAC). Subsequently, discussions between the NBA and ASCIA led to the eligibility criteria being included in the HAE Management Plan and updated following the introduction of Berinert SC. ASCIA reported holding some reservations on the restrictiveness of the criterion, however, were motivated to have it included and maintained as part of the national blood arrangements ensuring no-cost availability for their patients with HAE.

In Australia, various products have been made available for HAE treatment. Icatibant has been in use since 2012 and Berinert® IV since 2016, for the treatment of acute HAE attacks. Danazol was available through the Pharmaceutical Benefits Scheme (PBS) up until its withdrawal from the Australian market in January 2020 and had been the first line drug used for long term prophylaxis (LTP) of HAE. Berinert® SC, was added to the National Product Price List (NPPL) in March 2020 and lanadelumab was added to the PBS in December 2021, both are used for LTP of HAE.

Analysis undertaken by the NBA in 2021 showed that, since Berinert® SC was included as part of the national blood arrangements and there was a 7-fold increase in total spending of NBA funded C1-INH. This rapid increase in spending was the catalyst for this utilisation review.

The objectives of this review were (i) to describe the utilisation of NBA funded C1-INH in Australia since its inclusion under the national blood arrangements and (ii) to identify factors driving its increased demand. This review will assist to inform the NBA of the reason for the rapid increase in the demand of NBA funded C1-INH, and enable the NBA to determine whether this growth is appropriate in the context of guidelines for NBA funded access.

This review reports on the factors leading to the increase in C1-INH supply since it became publicly funded, and whether demand of C1-INH is likely to continue at recent levels. It is anticipated that information provided by this review will be used to inform subsequent projects, including any review of the guidelines for NBA funded access, supply planning, and as a potential resource in the assessment of any new treatments for HAE.

A mixed methods approach was used to analyse the information gathered via qualitative and quantitative processes. The quantitative data obtained from the NBA was analysed to present the trends in demand for Berinert® IV and SC alongside utilisation of other treatments for HAE over time. Quantitative information gathered from interviews, surveys and program documentation is analysed against the key review questions and reported accordingly.

Key Findings

The key finding of the utilisation review is that the combination of a higher number of patients transitioning to NBA funded Berinert® SC and then started on, or quickly transitioned to, a dose that was larger than that first envisaged, have been the greatest factors influencing the rapid and large increase in

the utilisation of Berinert® SC. The inclusion of patients who did not meet the criteria for NBA funded access to Berinert® SC was viewed as a quality-of-life decision by the clinicians.

Specific factors that led to this rapid increase in the utilisation of Berinert® SC include:

- Withdrawal of danazol from the market, the predominant HAE LTP treatment, and introduction of Berinert® SC as an alternative
- For patients using Berinert® IV for prophylaxis, the subcutaneous preparation offered much greater ease in self-administration, driving up utilisation of Berinert® SC (Berinert® IV for LTP demand reduced substantially)
- Additionally, the transition from Berinert® IV to Berinert® SC for prophylaxis may have been related to the fact that the intravenous preparation is not registered for LTP whereas the subcutaneous preparation is (noting this was not confirmed by any clinicians interviewed)
- While on danazol, some patients still required the supply of icatibant and Berinert IV for effective control of their HAE symptom while the move to Berinert® SC reduced this need for additional acute treatments
- Clinicians and consumers reporting better control of HAE and quality of life benefits associated with Berinert® SC
- The combination of limited side effects and the greater ease in self administration resulted in Berinert® SC being considered a superior product by clinicians and patients and hence becoming the LTP treatment of choice. Accordingly, many patients were progressively transferred to Berinert® SC over time including those who were outside of the established eligibility criteria for NBA funded Berinert® SC of 'at least 8 attacks per month'
- Whilst many patients commenced with the ASCIA guidelines agreed dose of 40IU/kg, clinicians reported shifting many patients to a 60IU/kg dose within a short period of time to address breakthrough symptoms of their HAE. In fact, some clinicians reported commencing patients on a 60IU/kg dose. Based on their clinical experience and understanding of the protocol in other countries, it was reported that the 60 IU/kg dose provides better control of HAE in most patients.

Specific findings for each of the review themes are summarised below:

Supply and Product-Mix

From 2020 onwards, the data clearly demonstrates a substantial increase in the supply of Berinert® SC nationally as well as for all jurisdictions, except the Northern Territory and Tasmania. This increase in the demand of Berinert® SC is noticeable alongside reduced supply of danazol and Berinert® IV. The shift of patients who were on Berinert® IV as prophylaxis treatment to Berinert® SC as the new first line LTP treatment contributed to this increased utilisation. Use of icatibant as an acute treatment has been steady overtime and Berinert® IV demand also stabilised in FY 2021-22.

Since December 2021, lanadelumab in sub-cutaneous form has been available through the PBS in Australia as a LTP treatment for HAE. Clinicians believe that lanadelumab is more convenient for patients, needing to be administered less frequently (once in two weeks compared to 2-3 times a week for Berinert® SC) and is subject to less stringent PBS access criterion (i.e. patient is eligible if suffering 12 attacks over 6 months compared to 8 attacks per month for Berinert® SC). Consultations with clinicians and the available data indicate a shift from Berinert® SC to lanadelumab and prescribers indicate that this trend will continue over time.

Patient Population

The review aimed to ascertain what the patient population with HAE in Australia was and were there any factors relating to the patient population that had driven the increased utilisation of NBA funded C1-INH. Estimating an accurate HAE patient population and hence the cohort who should be using NBA funded

C1-INH was challenged by (i) a lack of systematic data gathering on individual patient level utilisation, (ii) not all patients register as members of the HAE consumer organisation (HAE Australasia) and, (iii) there is limited epidemiological data on the prevalence of HAE across Australia. In order to obtain accurate population data and improve understanding of the HAE patient population, consideration could be given to an epidemiological study or a patient registry.

Despite the lack of available data, through consultations and various approaches to estimating the HAE population, it was estimated that there are likely between 300-500 people with HAE in Australia. Through the same processes, it is estimated that around 100 people with HAE are prescribed Berinert® SC regularly.

Two other factors explored as part of the review were the potential impact of COVID 19 on the HAE population (i.e. increased attacks or breakouts due to associated stress) and whether the HAE population growth was a driver of increased C1-INH utilisation. The conclusion from the consultations with specialists and HAE Australasia was that neither of these were drivers of increased utilisation.

Prescribing

The mandatory completion of all fields of the 'Order Form' available from CSL Behring governs the supply of C1-INH funded under the national blood arrangements. There was a strong consensus among stakeholders that this order form as the only mechanism of governance for ordering an expensive blood product such as C1-INH, was insufficient. Concerns were also expressed regarding the capacity for readily gathering reliable and comprehensive prescribing and supply information that enables timely sharing of this data with the jurisdictions as joint funders (jurisdictions contribute 37%). The order form had an expanded number of data fields introduced in 2021, facilitating more comprehensive information to be collected and greater analysis at the patient level as needed. Despite this, there remained a strong view that the processes for prescribing and ordering NBA funded C1-INH should be reviewed ensuring better governance and patient safety and could include the use of existing information systems.

Prescribing guidelines for C1-INH have been established by ASCIA under its HAE Management Plan. The ASCIA guidelines reflect the criteria for NBA funded access to C1-INH. This review suggests that clinicians are aware of these guidelines including criteria for prescribing NBA funded C1-INH, but variation exists in following the components of these guidelines. In particular:

- *'patients experiencing at least 8 attacks per month'* to gain access to NBA funded C1-INH is reportedly not followed all of the time.
- *Prescribing 'a starting dose of 40IU/kg'* of Berinert® SC whilst followed by some clinicians for some patients is not the case for all patients.
- *'frequency of a patient review'* is observed by the clinicians most of the time.

Case-Review Process

As part of the guidelines for accessing NBA funded C1-INH, the ASCIA case review process is in place for clinicians to obtain approval for increasing the dose of Berinert® SC from 40IU/kg to 60IU/kg if effective control of HAE attacks is not achieved after four to six weeks. The clinicians seem to be aware of this case-review process however not many clinicians reported following the process, and limited evidence is available that would suggest it is being used.

Future Outlook

In the same way that there was a rapid transition to Berinert® SC due to the superior benefits over other LTP treatments at the time, the advice from clinicians supported by an analysis of LTP treatment data demonstrates that this is similarly occurring with lanadelumab. Since it became made available under the PBS in December 2021, clinicians report that they have discussed and subsequently transitioned most of their patients to lanadelumab making it the LTP treatment of choice. Overall, it was reported by clinicians that there might be up to a 75-80% reduction in the requirements of Berinert® SC over time.

Of those remaining on Berinert® SC, the majority are reportedly children and women in pregnancy as well as during breastfeeding, however, this may also change should lanadelumab be concluded as safe for these cohorts. A very small minority have elected to stay with Berinert® SC on the basis there is no compelling reason for them to change.

The consultations suggest that the future of HAE control and management will increasingly be based on pharmaceutical products rather than blood products.

Recommendations

1. *Review the system of governance for ordering and recording the supply of NBA funded C1-INH:* The processes for ordering NBA funded C1-INH should be reviewed ensuring better governance and patient safety and could include the use of existing (BloodSTAR was suggested by a number of stakeholders as a potential template) or a new information system to enable more expedient reporting. This will improve the current mechanism for supply data collection enabling the NBA to undertake comprehensive, quality, and timely data analysis and to identify utilisation trends in real-time.

2. *Review the guidelines for accessing NBA funded C1-INH:* Given the broad non-compliance with the criteria for accessing NBA funded C1-INH and given their inclusion within the ASCIA guidelines for HAE management, the criteria should be reviewed in collaboration with the HAE sub-committee of ASCIA and other relevant stakeholders.