# **Medical Services Advisory Committee (MSAC)**

# **Public Summary Document**

Application No. 1714 – National Blood Authority listing for Obizur® (susoctocog alfa) for treatment of bleeding episodes with acquired Haemophilia A

**Applicant: Takeda Pharmaceuticals Australia Pty Ltd**

**Date of MSAC consideration: 30-31 March 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

## 1. Purpose of application

An application requesting that Obizur® (susoctocog alfa) be publicly funded under the National Blood Arrangements via the National Product Price List (NPPL) for the treatment of bleeding episodes in adult patients with Acquired Haemophilia A (AHA), was received from Takeda Pharmaceuticals Australia Pty Ltd by the Department of Health and Aged Care.

## 2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the addition of Obizur to the National Blood Authority’s (NBA’s) NPPL for first-line monotherapy treatment only, of spontaneous bleeding episodes in adult patients with AHA. MSAC noted its advice would inform the Jurisdictional Blood Committee (JBC) and any potential recommendation to all Health Ministers to include Obizur on the NPPL.

MSAC noted the clinical claim of non-inferiority of Obizur use in all lines of therapy in terms of safety and effectiveness against both comparators, NovoSeven® RT and FEIBA NF®, was uncertain due to the lack of high-level comparative evidence but was likely non-inferior for first line use. MSAC acknowledged that, due to the rarity of AHA, it was unlikely that any randomised controlled trials would be forthcoming to provide greater certainty of evidence.

MSAC considered that the cost-minimisation analysis and estimated financial impact were difficult to assess with confidence due to the limited supporting published evidence, confounding factors in estimating equi-effective doses, the small number of patients predicted to be treated per year, their diverse aetiologies, and the highly variable presentation and clinical course of a bleeding episode (among other issues). Nonetheless, MSAC considered there to be clinical need for improved therapies for AHA such as Obizur and that provisions could be implemented such as improving monitoring of the use of each therapy (including cost per bleeding episode) and post-treatment outcomes via the Australian Bleeding Disorders Registry (ABDR), a risk share arrangement (RSA) with the applicant to avoid overspending on the budget, and a review of all treatment utilisation after two years post-implementation.

| Consumer summary |
| --- |
| This is an application from Takeda Pharmaceutical Australia requesting that Obizur® (susoctocog alfa) be publicly funded under the National Blood Arrangements through the National Product Price List for the treatment of bleeding episodes in adult patients with acquired haemophilia A.  Acquired haemophilia A (AHA) is a condition where patients present with spontaneous bleeding (bleeding for no reason or without an obvious injury) despite having no history of a bleeding disorder. The condition can appear late in life and is different to congenital haemophilia A where patients are born with the condition. Obizur is not proposed to be used in the management of patients with congenital haemophilia A. Patients with AHA have the protein needed for blood clotting (Factor VIII) but develop antibodies against this protein (autoantibodies) which inactivates it (stops it from working). As Factor VIII becomes inactivated, the blood does not clot as quickly as it should and patients may experience abnormal bleeding following surgery or injury, or develop spontaneous bleeding, which can range from minimal requiring no treatment to severe or life-threatening requiring hospitalisation.  Obizur is a manufactured product (rather than sourced from donated blood) that replaces the action of the inactivated Factor VIII in patients with AHA but is not affected by the autoantibodies that cause AHA. Furthermore, unlike existing treatments, Obizur treatment allows for the patient’s clotting activity to be measured in response to treatment, which assists with guiding dosing and monitoring.  MSAC considered that, if Obizur is used alone as a first-line (first choice) therapy for bleeding, it appears to be as safe and effective as other available treatments, and there is a high need for new treatment options such as Obizur to help treat bleeding in these patients. MSAC noted that there are very few patients (around 100) in Australia with AHA and even fewer (less than 20) who require hospitalisation and treatment for a bleed each year. MSAC could not confidently assess Obizur’s value for money because supporting evidence was limited (due to how rare the condition is), but MSAC advised that the use of Obizur should be monitored and reviewed after two years to ensure that it remains effective and safe and is good value for money. MSAC’s advice to the Commonwealth Minister for Health and Aged Care MSAC supported Obizur being publicly funded through the National Product Price List as a first-line therapy. Obizur as a first-line treatment appears to be as safe and effective as other treatments. The use, effectiveness and safety of Obizur should be reviewed after two years. |

## 3. Summary of consideration and rationale for MSAC’s advice

MSAC noted that this application from Takeda Pharmaceuticals Australia Pty Ltd was requesting that Obizur® (susoctocog alfa) be publicly funded under the National Blood Arrangements through the NBA’s NPPL for the treatment of bleeding episodes in patients with AHA. MSAC noted that consultation feedback sought from professional societies were strongly supportive of listing and agreed that advances in available treatments for these patients was needed.

MSAC noted that AHA is a rare but life-threatening autoimmune bleeding disorder where patients develop autoantibodies to coagulation Factor VIII (FVIII). Patients typically present with a sudden bleeding event. MSAC noted that there are two peaks for the disease: during pregnancy, and in older (around 75 years of age and older) people (more often in males than females). MSAC noted that approximately 40–50% of AHA patients have an identifiable underlying condition such as autoimmune diseases and cancer or the condition is pregnancy-associated.[[1]](#footnote-2)

MSAC noted that Obizur is a purified, recombinant porcine FVIII molecule (rpFVIII) that replaces missing human FVIII in the coagulation pathway. The sequence of Obizur is sufficiently different to human FVIII to minimise cross-reactivity with the inhibitors directed against human FVIII. Additionally, MSAC noted that Obizur is already being used in Australia for treatment of spontaneous bleeding episodes in patients with AHA without a fixed funding mechanism.

MSAC noted there is a clinical need for access to improved therapies that allow better monitoring of treatment response, particularly because direct measurement of coagulation in response to treatment could reduce thrombotic complications for patients with AHA, particularly those with underlying cardiovascular disease. MSAC noted that the proposed population is restricted to patients with AHA only (congenital haemophilia A was not within the scope of this application), excluding those with anti-pFVIII inhibitor levels >20Bethesda Units (BU). MSAC noted there is a small prevalent population; of the 92 patients who were known to have AHA in Australia in 2019–20 according to the ABDR annual report, 12 (13%) required haemostatic treatment.

MSAC noted that treatment of AHA involves treating the underlying disease, usually with steroids with or without cyclophosphamide (or similar) in addition to the acute management of bleeding episodes. MSAC noted that approximately 30% of people who bleed do not need haemostasis treatment, while approximately 16% of all patients on the register need treatment each year. MSAC noted that up to one-third of patients with AHA die either from their underlying disease, bleeding or complication of treatment (usually as a result of high doses of immunosuppressants).

MSAC noted that the two nominated comparators were bypassing agents (BPAs): NovoSeven® RT (recombinant activated Factor VII [FVII]) and FEIBA NF® (FVIII inhibitor). MSAC noted that there is no ability to monitor treatment response or guide dosing in patients when BPAs are given to treat an acute bleed, and repeated dosing is based on the observed clinical response. In contrast, because Obizur replaces FVIII, clinicians can monitor clotting activity by the activated partial thromboplastin time (APTT) (MBS item 65120) to guide dosing and assess response to treatment. Improved monitoring may mitigate the risk of bleeding and serious adverse events (SAEs) associated with high clotting activity, such as thrombosis. MSAC noted that patients can also develop antibodies to rpFVIII, so these have to be tested for before Obizur treatment starts (without delaying treatment); if a patient is found to have elevated anti-rpFVIII antibodies, Obizur would be ceased and BPAs used instead.

MSAC noted that the initial dose for Obizur proposed in the applicant-developed assessment report (ADAR) (100–200 Units/kg) was less than the initial dose currently recommended in the Product Information (PI) (200 Units/kg). MSAC agreed with ESC’s advice that “based on the evidence presented … an initial dose between 100 and 200 Units/kg may be appropriate, relative to the clinical judgement of the treating practitioner and individual patient circumstance (including assessment of laboratory results)”. MSAC also considered that clinical practice has evolved, noting the presented evidence, and consultation feedback, to support a lower starting dose as well as the ability to directly monitor APTT during treatment. MSAC also noted that the European Summary of Product Characteristics for Obizur contains a statement that permits a lower initial dose than 200 units/kg in patients who test negative for anti-rpFVIII antibodies at baseline, but that clinical response should be closely monitored.

MSAC noted the ADAR did not propose a line of therapy for Obizur in the clinical management algorithm. MSAC noted that the Baxalta Advisory Board (in March 2017) and international management guidelines (from 2020) both suggested Obizur as an alternative first-line therapy. MSAC also noted that feedback from professional societies was that Obizur should be used only as a first-line therapy in Australia. MSAC noted the pre-MSAC response agreed with ESC that the clinical management algorithm from the UK-based National Health Service Policy on Obizur treatment for a bleeding episode in people with AHA[[2]](#footnote-3) should be adapted for use in Australia. The applicant stated that they would “contribute to the communication of any Australian guidelines developed to guide treatment with Obizur in clinical practice”.

MSAC noted that the evidence base presented, which included 16 case series and 1 retrospective cohort study, was limited in terms of the lack of direct comparative studies for the intervention versus the comparators and all 17 studies presented were at a high or very high risk of bias. The retrospective cohort study, which used Medicare claims data, was the only study that directly compared Obizur versus NovoSeven and its survival analysis was provided as evidence for all-cause mortality (measuring the probability of death as the outcome). MSAC acknowledged that the low patient numbers presented challenges in generating reliable data such as large comparative studies like randomised controlled trials (RCTs). MSAC also noted that there are no data on the use of Obizur in pregnant and lactating women or its effect on fertility, and there are no data on use in patients less than 18 years of age. However, MSAC agreed with ESC that “…further (clinical trial) data may be unlikely to be available in the future” because of small patient numbers, and that “…clinical effectiveness and safety of Obizur appears to be non-inferior compared with each of the two comparators”. MSAC also noted that the pre-MSAC response acknowledged that there is uncertainty with the non-inferiority claim.

Regarding comparative safety, MSAC considered that there was insufficient evidence to support the claim of non-inferiority, due to inconsistent results (both inferior and superior) across naïve indirect comparisons, differences between studies and small patient numbers. This included evidence related to risk of treatment-related thrombosis (inconsistent results), serious adverse events (SAEs, inconsistent results) and treatment related mortality (no difference). For all-cause mortality, MSAC noted that patients receiving Obizur were 14% more likely to die versus NovoSeven, and 10% more likely to die versus FEIBA. However, the study using Medicare claims data suggested that patients receiving Obizur had a higher probability of survival. Overall, MSAC considered that it was difficult to disentangle safety outcomes due to therapy from confounding factors, but that there was no clear evidence of inferiority for Obizur when restricted to first-line therapy.

MSAC noted bleeding resolution was used to measure the comparative effectiveness of Obizur versus the comparators however, MSAC interpreted these estimates with caution since the studies varied in their reporting on final outcomes of bleed resolution (‘non-resolved’ bleeds were reported but the outcome not described further) or of death and there was a lack of reporting on time to resolution of a bleed. MSAC noted that patients receiving Obizur were 8% and 11% less likely to have their primary bleed resolved versus NovoSeven and FEIBA, respectively. MSAC noted the ADAR claimed this result may be because more patients were receiving Obizur as second-line therapy in the Obizur studies and therefore they were more likely to be sicker. MSAC noted the ADAR provided a subgroup analysis for first-line treatment using Obizur that showed no significant differences between treatments for primary bleeds resolved.

For total number of bleeding episodes resolved, MSAC noted that Obizur patients were 9% less likely to have total number of bleeding episodes resolved versus NovoSeven. However, there was no difference versus FEIBA, and no difference if Obizur is used as a first-line therapy versus NovoSeven. MSAC noted that there was no between-group difference for the surrogate outcome of positive bleed rate at 24 hours versus NovoSeven. MSAC noted that Obizur studies used APTT to determine the positive rate, while NovoSeven studies used clinical judgement. MSAC considered that monitoring APTT may show a response more quickly than a clinically recognisable response.

MSAC considered in relation to the clinical claim that, if Obizur is used as a first-line monotherapy treatment for spontaneous bleeding episodes, there is evidence to support the claim of non-inferior effectiveness compared to both comparators. In terms of safety, MSAC considered that Obizur was likely to have acceptable safety compared to both.

MSAC noted that a cost-minimisation approach (CMA) was performed for each comparator alone versus Obizur for the economic evaluation, but in practice both BPAs may be used in managing an individual’s bleeding event. The proposed price per vial of Obizur was based on weighting the respective cost-minimised prices by the observed distribution of use of each comparator. MSAC noted ESC’s advice pertaining to the areas of uncertainty with the economic evaluation. MSAC noted that the incremental cost-effectiveness of BPAs versus no intervention has not been established and the applicant did not provide a comparison for Obizur versus no intervention as part of the economic evaluation. MSAC noted ESC’s advice that without an established cost-effective price for BPAs, the CMA applied for Obizur versus each comparator provides little confidence in the assumption that the proposed price per vial for Obizur represents an incremental benefit relative to no intervention.

MSAC also noted the multiple issues with the assumed equi-effective doses raised in the evaluation and affirmed by ESC that introduced uncertainty into the economic evaluation. MSAC noted the evidence base had wide variation in baseline patient characteristics and were not adjusted for when the ADAR established their equi-effective doses. MSAC also noted the equi-effective dose for Obizur estimated by the ADAR was based on successfully resolved bleeds, but it was uncertain whether this also applied to the comparators, and this outcome was inconsistently reported across studies. MSAC agreed with ESC and did not accept the sensitivity analyses performed during the evaluation, considering these estimates to be too conservative since they excluded studies that used an initial dose of Obizur <200 U/kg. MSAC noted ESC’s advice and calculation that, based on the acceptance of a lower initial dose, the revised equi-effective dose calculations in the pre-ESC response and the new NPPL prices, the cost-minimised weighted price for Obizur may be $[REDACTED] per vial.

MSAC noted the presentation of a spontaneous bleeding episode and response in treating patients in these circumstances varies greatly and would have a significant impact on the reliability of the financial estimates. MSAC noted that the financial impact was most sensitive to the assumed equi-effective doses. The total dose of BPAs dispensed that was used in the ADAR was substantially higher than the actual dispensed amounts reported in the ABDR 2019–20 annual report. MSAC noted there was also uncertainty in the time for bleeding to resolve yet the ADAR assumed no differences between the therapies in the duration of treatment for a bleed. Given this notable difference being identified in the evaluation, there is low confidence in the accuracy of the cost of monitoring (especially as Obizur requires additional tests to monitor response) and hospital length of stay.

MSAC noted the ADAR used literature (Holstein et al. 2020) to estimate the number of bleeding episodes per patient that would be treated each year (4.68) for the base case analysis. However, the evaluation estimated using actual dispensed amounts from the ABDR and the ADAR estimated dose per bleed, that the number of bleeds per year treated with NovoSeven and FEIBA are 2.21 and 1.17 respectively. MSAC considered the scenario analysis using the volume of products dispensed to likely be a more accurate estimate of the total cost to the NBA which represents a lower annualised bleeding rate, rather than that based on the higher annualised bleeding rate described in the literature.

MSAC considered that despite the uncertainties in the economic modelling and financial impact estimates of adding Obizur to the NPPL, that current available evidence had at least demonstrated Obizur to have non-inferior effectiveness and was acceptable in terms of safety relative to its comparators in first-line treatment of spontaneous bleeding episodes in adults with AHA and therefore, supported public funding for Obizur in the first-line setting.   
MSAC considered the low patient numbers in this proposed population and need for patients with this rare condition to have access to public funding for novel innovative therapies in coming to their decision. To address some of the financial uncertainties, MSAC suggested some provisions that should be implemented to mitigate these risks and improve data collection.

Following advice from ESC, MSAC noted that the NBA could consider implementing a risk share arrangement (RSA) with the applicant that includes **price reductions on Obizur to address the risk of the average dose per patient per bleed being higher in practice than was assumed in the ADAR**. MSAC noted that the pre-MSAC response agreed with ESC’s advice on the need to determine the average dose per patient per bleed (all bleeds, resolved and unresolved) in practice for Obizur, NovoSeven and FEIBA, or combinations thereof. MSAC noted that the applicant had requested data from the NBA on the average dose per bleeding episode for the comparators however, they were unable to provide this level of data as it is not currently captured in the ABDR (it captures total amount dispensed for the products),

MSAC considered that the ABDR dataset should be updated to better capture utilisation and clinical outcomes of patients with AHA who have a bleeding episode as well as to determine a more accurate estimate for dose per patient per bleed for all utilised therapies in all bleeds (which may contribute to determining a cost-effective price for existing therapies). MSAC also considered that the dataset should capture duration of treatment, hospital stay and death as part of the safety outcomes. MSAC noted that the ABDR is currently estimated to capture more than 90% of patients in Australia diagnosed with AHA. Additionally, MSAC considered that insights could be obtained from patients to understand their experiences during treatment and how the condition presents for them individually.

MSAC considered that a post-implementation review should be conducted 24 months following public funding, to consider updated data on efficacy, safety and financial impact.

MSAC confirmed ESC’s advice that haematologists should be the sole prescriber for Obizur and noted that patients with AHA are generally managed in specialist centres (such as Haemophilia Treatment Centres (HTC)). MSAC advised that Obizur cannot be regarded as a complete substitute for BPAs, as there is a need for alternative treatments when anti-pFVIII inhibitor levels are >20 BU.

## 4. Background

MSAC has not previously considered Obizur for the treatment of bleeding episodes in adult patients with AHA.

In 2016, Takeda Pharmaceuticals Australia Pty Ltd (previously Baxalta Australia) submitted a Schedule 4 application to the NBA for Obizur to be included on the NPPL. An addendum to the Schedule 4 submission was further provided in 2017.

In 2020, the NBA conducted a Cycle 1 multi-criteria analysis (MCA) evaluation which provided a description of the proposal, followed by a PICO and a high-level literature review. The MCA concluded that uncertainties remained regarding whether Obizur will offer incremental health outcomes or safety benefits compared to BPAs and whether there will be cost savings or additional costs. Therefore, the NBA, on behalf of the JBC, referred the Obizur application to MSAC for a health technology assessment (HTA) to address these uncertainties. The MSAC Executive were consulted on the pathway for consideration and advised at its April 2022 meeting, that the Obizur application could by-pass PASC and lodge an ADAR directly, considering that a clearly defined PICO was included in the MCA.

A summary of how the ADAR and pre-ESC response has addressed concerns raised by the MCA evaluation, the MSAC Executive and the Commentary, is shown in Table 1.

Table 1 Summary of application concerns

| Components | Matter of concern | How the current assessment report addresses it |
| --- | --- | --- |
| Intervention | The place of Obizur in the treatment algorithm is uncertain as to whether it should be used first-line or second-line after bypassing agents, or in combination. | The amalgamated evidence has been separated into one line of therapy only. Sequential therapy is not assessed. |
| The initial dose used in practice (approximately 10% of the estimated total dose per bleed) does not reflect the dosing in the TGA product information | Refers to clinical advice that the first dose recommended in the Product Information has evolved from first registration. |
| Comparator | The MSAC Executive advised that the ADAR should estimate the incremental cost-effectiveness of Obizur over no intervention as an additional analysis to Obizur vs BPAs. | This was not addressed as the Applicant reasoned that BPAs are standard of care for first-line treatment of acute bleeds for AHA. |
| Clinical effectiveness | The National Blood Authority considered there was uncertainty regarding whether Obizur will offer incremental health outcomes or safety benefits compared to BPAs. | The applicant has conducted unadjusted naïve comparisons of safety and performance for Obizur vs. NovoSeven and Obizur vs. FEIBA. However, not all outcomes of the MCA were covered. |
| The outcome of achieving haemostasis following Obizur is not consistently reported for all patients in the identified publications. | Where able, the final outcome of bleeding is reported, but uncertainty remains as to the poorly defined outcome of ‘unresolved bleeding’. |
| Impact of non-therapy costs | Difference in rate of thrombosis by therapy type has been assessed, but not other hospitalisation costs.  There is no assessment of length of stay or associated costs for patients who received FEIBA and NovoSeven. |
| Cost-effectiveness | The National Blood Authority considered there was uncertainty as to whether there will be cost savings or additional costs. | The applicant has conducted a cost-minimisation analysis for Obizur vs. NovoSeven and Obizur vs. FEIBA. The applicant also presented financial implications of listing Obizur. |
| Financial analyses | The MSAC Executive advised the estimation of cost-offsets from substituting treatment with BPAs should also form part of the financial analyses. | The applicant included the cost-offsets from substituting treatment with BPAs as part of the financial analyses. |

AHA = Acquired Haemophilia A; BPAs = bypassing agents; MCA: Multi-criteria analysis; MSAC = Medical Service Advisory Committee

## 5. Prerequisites to implementation of any funding advice

Obizur is included on the Australian Register of Therapeutic Goods (AUST R 236475, effective from 29/04/2016).

Two tests are currently required to direct AHA treatment: isolated prolonged activated partial thromboplastin time (APTT) (covered under the broader MBS item 65120 for blood clotting testing) and quantitation of FVIII concentration and anti-FVIII inhibitors (MBS Item 65150). Treatment with Obizur requires an additional test for monitoring of anti-porcine FVIII (anti-pFVIII) concentration, required prior to, or during, treatment (MBS Item 65159).

There are reporting policies in place for high-cost care for coagulation disorders, including AHA, to meet the requirements of the Blood Supply Stewardship Policy*[[3]](#footnote-4)*. This would be relevant to Obizur, as well the comparator treatments.

## 6. Proposal for public funding

Obizur is a B-domain deleted recombinant derived antihaemophilic factor VIII (rpFVIII), porcine sequence. Obizur is available as lyophilized powder for solution in single-dose vials containing nominally 500 units per vial. Once dissolved, Obizur is delivered via intravenous injection.

Obizur is a haemostatic agent for on-demand treatment of acute bleeds in patients with AHA. The protein structure of Obizur is similar-enough to human FVIII that it increases FVIII clotting activity, however Obizur is sufficiently dissimilar in structure to evade anti-FVIII inhibitors. Administration of Obizur aims to control and cease the bleeding event.

The ADAR is seeking listing of Obizur on the NPPL for the treatment of bleeding episodes in adult patients with AHA. The proposed population was informed by the following TGA indication for Obizur: “*for the treatment of bleeding episodes in adults with acquired haemophilia A. Safety and efficacy of OBIZUR have not been established in patients with baseline anti- porcine factor VIII inhibitor titre greater than 20 BU., OBIZUR is not indicated for the treatment of congenital haemophilia A or von Willebrand disease*” (Public Summary ARTG 236475).

The ADAR proposed that the initial dose may be given at a range of 100 to 200 U/kg, depending on the treating clinician’s preference however, the PI recommends an initial dose of 200 U/kg and states that “initial dosing below the recommended 200 U/kg has been associated with lack of efficacy”. The ADAR stated that utilisation of an initial dose in the range of 100 to 200 U/kg reflects current clinical practice and cited studies 241302 and 241501 presented for TGA registration and Ellsworth et al (2020)[[4]](#footnote-5), initiated Obizur at 100 U/kg and suggests no loss in efficacy or safety. This claim is based on a naïve comparison of studies.

The ADAR-proposed price for Obizur is $[REDACTED] per 500-unit vial. The ADAR based this upon a weighted average of the cost per vial resulting from the cost-minimisation approaches (CMAs) versus NovoSeven (78%) and FEIBA (22%) with the current market share serving as the weights. At present, the contracted arrangements for NovoSeven and FEIBA are currently under review. As a result, the proposed price for Obizur may change.

Testing of FVIII concentration and APTT is required at the start/prior to treatment with Obizur and throughout the treatment period. The PI recommends that APTT is assessed at 30 minutes and 3 hours after the initial dose of Obizur, and 30 minutes after subsequent doses. Testing for anti-pFVIII is required at the start/prior to treatment with Obizur and at any point where treatment is not efficacious, that is, to test for neutralising inhibitor development directed against Obizur. The relevant MBS items are described in Table 2 below.

Table 2 MBS item descriptors

| Category 6 – PATHOLOGY SERVICE Group P1 - Hematology |
| --- |
| MBS 65120  Prothrombin time (including INR where appropriate), activated partial thromboplastin time, thrombin time (including test for the presence of heparin), test for factor XIII deficiency (qualitative), Echis test, Stypven test, reptilase time, fibrinogen, or 1 of fibrinogen degradation products, fibrin monomer or D-dimer - 1 test  **Fee:** $13.70 **Benefit:** 75% = $10.30 85% = $11.65 |
| MBS 65150  Quantitation of von Willebrand factor antigen, von Willebrand factor activity (ristocetin cofactor assay), von Willebrand factor collagen binding activity, factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, factor XIII, Fletcher factor, Fitzgerald factor, circulating coagulation factor inhibitors other than by Bethesda assay - 1 test  (Item is subject to rule 6)  **Fee:** $70.90 **Benefit:** 75% = $53.20 85% = $60.30 |
| MBS 65159  Quantitation of circulating coagulation factor inhibitors by Bethesda assay - 1 test  Fee: $70.90 Benefit: 75% = $53.20 85% = $60.30 |

## 7. Population

The proposed population for Obizur includes adult patients (≥18 years) with AHA who require on-demand treatment of an acute bleeding episode. Consistent with the TGA approved indication, the proposed population excludes patients with Congenital Haemophilia A (CHA) or von Willebrand disease, and patients with AHA and anti-pFVIII inhibitor levels greater than 20 Bethesda units (BU), as there is currently insufficient information on how effective Obizur is in this population. Obizur is not indicated for routine, or pre-operative, bleeding prophylaxis.

Haemophilia A is a disease where an individual has an insufficient concentration of active blood clotting Factor VIII (FVIII), resulting in bleeding episodes which may not resolve due to the interrupted blood-clotting process. Haemophilia A may be classified as congenital (CHA) or acquired (AHA). CHA is a genetic disorder caused by missing or defective FVIII.

AHA is a very rare autoimmune condition occurring in association with a wide variety of other underlying conditions whereby patients spontaneously develop neutralising inhibitors to previously sufficient blood clotting FVIII. The disease is characterised at presentation by bleeding episodes (spontaneous or traumatic) in individuals with no personal or familial history (of CHA).

AHA is treated with immunosuppressive therapy (IST) and haemostatic therapy. IST is used for eradication of inhibitors. IST may result in significant complications such as infection, neutropenia and diabetes. There is also the risk of relapse, which is highly-variable, depending on regimen and other underlying factors. Haemostatic therapy using FEIBA and/or NovoSeven is used on-demand to resolve acute bleeding episodes or may be given as prophylaxis prior to surgery. The major risk of any haemostatic treatment is venous or arterial thrombosis. Many AHA patients have underlying cardiovascular issues which can increase the risk of thrombosis.

In the Australian context, data from the Australian Bleeding Disorders Registry (ABDR) Annual report (2019-2020)[[5]](#footnote-6) revealed that there were 92 patients with AHA in 2019-2020. Of these, 12 (13%) required haemostatic treatment. The majority of patients with AHA tend to be over the age of 65 years. Tay et al. 2009[[6]](#footnote-7) reported a median age of 78 years and 74 years in Dix at al. 2022[[7]](#footnote-8).

## 8. Comparator

The nominated comparators are NovoSeven and FEIBA, which are the two FVIII BPAs used in Australia for treating bleeds in patients with AHA. Both therapies work by circumventing the need for FVIII replacement in the blood-clotting pathway. NovoSeven and FEIBA are currently listed on the NPPL (Table 3).

Obizur is proposed as an alternative to both NovoSeven and FEIBA. The ADAR hasn’t specifically nominated a line of treatment for Obizur. However, in the published literature, Obizur has been used as a first-line treatment as well as in subsequent lines. The major difference between Obizur and BPAs is that Obizur requires additional monitoring of FVIII activity throughout treatment as well as establishment that the patient has low anti-pFVIII titre as determined by the Nijmegen-Bethesda assay. While this is an additional cost, the FVIII monitoring requirements for Obizur confers benefit in bleeding management as it can indicate the efficacy of treatment.

Table 3 National Product Price List for comparators

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Supplier** | **Product Name** | **Product Type** | **Presentation** | **Price (updated pricea)** |
| Novo-Nordisk  Pharmaceuticals | NovoSeven | Factor VIIa (recombinant - imported) | 1 mg | $1,351.11 ($1,250.00) |
| 2 mg | $2,702.22 ($2,500.00) |
| 5 mg | $6,755.55 ($6,250.00) |
| 8 mg | $10,808.88 ($10,000.00) |
| Takeda  Pharmaceuticals  Australia | FEIBA | Factor VIII  Activated Prothrombin Complex Concentrate  APCC) (plasma derived - imported) | 500 U | $1,200.00 ($1,140.00) |
| 1000 U | $2,400.00 (NA) |
| 2500 U | $6,000.00 ($5,700.00) |

Source: Compiled 1 July 2022 from <https://www.blood.gov.au/national-product-price-list>

a Updated price of comparator product at 1 January 2023. Impact of updated prices has been tested in economic and financial analyses.

NA = product is not listed in the updated National Product Price List

The MSAC Executive advised at its April 2022 meeting considering the HTA pathway for Obizur, that the ADAR should estimate the incremental cost-effectiveness of Obizur over no intervention as an additional analyses to Obizur versus BPAs. This was because the cost-effectiveness of BPAs listed on the NPPL for the treatment of bleeds in patients with AHA has not been established (noting BPAs are used in other bleeding disorders). This was acknowledged in the ADAR; however, analysis was only conducted for Obizur versus BPAs, the ADAR stating that a comparison against no intervention was impractical as BPAs were the established standard of care for first-line treatment of AHA and there was considered no equipoise, or clinical evidence available, for no intervention as a comparator.

The evaluator considered this approach to be reasonable, identifying a natural history study of 16 patients with AHA which reported a mortality rate of 12.5% due to haemorrhage over 31 months of follow-up[[8]](#footnote-9). Issues with small sample size notwithstanding, this study is not representative of current clinical practice. Collins et al. 2012[[9]](#footnote-10) states that standard of care for acute bleeds in patients includes treatment with BPAs.

## 9. Summary of public consultation input

Consultation input was received from three organisations and one individual specialist. The organisations included one consumer organisation and two professional organisations:

* Haematology Society of Australia and New Zealand (HSANZ)
* Australia Haemophilia Centre Directors’ Organisation (AHCDO)
* Haemophilia Foundation Australia (HFA)

All consultation input was supportive of public funding of Obizur. All input noted the benefits of Obizur is the ability to monitor FVIII levels to guide treatment. These patients often present with critical bleeding and having the ability to monitor the levels may offer patients more personalised therapy at a critical time where they are at high risk of mortality. HSANZ stated Obizur offers non-inferior haemostatic control compared with NovoSeven and FEIBA.

HFA considered that Obizur was an important advance in the treatments available to patients with AHA and that the ability for clinicians to titrate the dose to appropriately manage a patients bleed was important in improving patient safety by lowering the risk of thrombosis.

HSANZ noted a disadvantage of Obizur is the additional blood test needed in the treatment process versus treatment with NovoSeven or FEIBA however, they considered this can be taken with other daily bloods so is unlikely to be significant to the patient. Another disadvantage that was noted by AHCDO and the individual specialist was the potential for Obizur to become ineffective in some patients due to the development of anti-rpFVIII antibodies, but BPAs could then be used.

Following ESC’s consideration, further input was sought from professional organisations to assist in informing decision making. HSANZ, AHCDO and the Thrombosis and Haemostasis Society of Australia and New Zealand (THSANZ) provided responses to these additional questions:

1. *Can you provide advice on whether an initial dose of Obizur below 200U/kg (which is below the stated dose recommended in the PI currently but what is being proposed by the applicant) would be considered appropriate and standard practice in the clinical management of a patient’s spontaneous bleed?*
2. *Can you provide advice on what line in therapy Obizur would be considered in the management of a patient’s spontaneous bleed (relative to NovoSeven and FEIBA)? The application form (p16) claims that Obizur will be used instead of the comparators however, this has not been clearly repeated through the application process.*
3. *Can you provide advice on what proportion of bleeding events would be expected to be managed with (i) Obizur alone, (ii) only FEIBA and NovoSeven, and (iii) combination of all three products?*

All responses to question 1. considered it appropriate and common from evidence and experience to start Obizur at a dose between 100 Units/kg and 200 Units/kg and noted that Obizur, opposed to BPAs, can be monitored and the dose can always be increased as needed to the desired effect for a presenting patient.

In response to question 2. all respondents unanimously agreed that Obizur would be utilised as the first line agent as monotherapy, in place of BPAs, to treat a patient for a spontaneous bleed. The respondents all stated that if Obizur monotherapy does not arrest bleeding, Obizur would be ceased and treatment with FEIBA and/or NovoSeven would be initiated.

All responses to question 3. Considered that Obizur alone would likely be the most common approach in treating patients for a spontaneous bleed, with a small number of instances where it may be clinically appropriate or needed to additionally administer BPAs if Obizur is ineffective in managing a bleed. THANZ considered this may occur in approximately 10% of patients based on published data.

HSANZ also noted that some patients may present at regional sites which may only have NovoSeven on hand so patients may be treated initially with NovoSeven while they are transferred to a larger centre, and then given Obizur during the rest of the course of treatment. HSANZ considered that the use of FEIBA will be largely replaced by Obizur since FEIBA has a drug interaction with the use of emicizumab and therefore various HTCs are reducing the stock they hold of FEIBA from their inventories.

## 10. Characteristics of the evidence base

The body of evidence for Obizur (k= 5) and the comparators (NovoSeven, k= 8; and FEIBA, k=5) was limited. There were 16 case series which were judged to have a “high” to “very high” degree of bias, as determined by the NHLBI Quality Assessment Tool For Case Series Studies[[10]](#footnote-11) (Table 4). The key sources of bias across studies were absent or incomplete descriptions of baseline characteristics, and heterogeneous definitions of efficacy outcomes. There was one retrospective cohort study (Batt et al. (2022)[[11]](#footnote-12)) which was judged to have a high risk of bias as determined by the ROBINS-I tool[[12]](#footnote-13). Key sources of bias related to the lack of details in the classification of treatment and diagnosis. This was due to the usage of data from the Medicare claims database, as opposed to patient medical records.

Overall, the evidence base presented in the ADAR was small and non-comparative. Given the rarity of the disease, better quality evidence is unlikely to become available in the future. Additionally, there are serious issues with regard to differences in classification of efficacy outcomes that hampers comparison of health outcomes across studies. This is due to lack of standardised endpoints within the field of research.

All 17 studies presented in the ADAR were restricted to patients who had AHA and were being treated for a bleed in a hospital setting. The majority of bleeds were largely due to spontaneous, traumatic or post-surgical causes, which fitted the proposed population. The population largely represented the elderly population, as opposed to gestational AHA. Median age range for Obizur studies ranged from 68–77 years; 59–80 years for NovoSeven; and 57.5–83 years for FEIBA,

Anti-pFVIII levels were reported in all studies of Obizur, one study of NovoSeven (NovoSeven CUP) and in one study of FEIBA (Sallah et al. (2004)[[13]](#footnote-14)). It is unknown how many patients in the other studies are suited to the proposed population in terms of having anti-pFVIII lower than 20 BU. This increases the uncertainty in the transitivity of the populations of the comparator studies to patients from that of Obizur.

Table 4 Key features of the included evidence

| References | N | Design/duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
| --- | --- | --- | --- | --- | --- | --- |
| Obizur | | | | | | |
| OBI-1-301 | 29 | Case series | *High* | Patients with AHA aged ≥ 18 years suffering from a serious bleed | Positive response rate (effective or partially effective control of bleeding) at 24 hr  Bleeding episodes successfully controlled, as assessed by the investigator  Serious Adverse Events | Yes |
| Study 241302 | 53 | Case series | *Very high* | Patients with AHA aged ≥ 18 years treated in a hospital setting | Incidence of treatment-related SAEs  Haemostatic effectiveness of Obizur in the treatment of bleeding episodes | Yes |
| Ellsworth et al. (2020) | 18 | Case series | *Very high* | Patients with AHA | Resolution of bleeding episode | Yes |
| Study 241501 | 50 | Case series | *Very high* | Patients with AHA aged ≥ 18 years treated in routine clinical practice (not specified) | Incidence of thromboembolic events  Haemostatic effectiveness of Obizur in the treatment of bleeding episodes  Safety | Yes |
| **Obizur vs NovoSeven** | | | | | | |
| Batt et al. (2022) | 166 | Retrospective cohort study | *Very high* | Patients with AHA aged ≥65 years treated with Obizur and/or NovoSeven | Probability of death | Yes |
| **NovoSeven** | | | | | | |
| EACH2 | 159 | Case series | *Very high* | Patients with AHA | Control of the primary bleeding episode  Safety | Yes |
| Amano et al. (2017) | 132 | Case series | *Very high* | Patients with AHA | Clinical response rate defined as patients with a markedly effective or effective haemostatic response  Safety | Yes |
| ACQUI-7 | 27 | Case series | *Very high* | Patients with AHA | Resolution of the primary bleed based on symptoms, pain and Hb levels  Safety | Yes |
| HTRS Registry | 68 | Case series | *Very high* | Patients with AHA | Resolution of bleeding episodes  Safety | Yes |
| NovoSeven CUP | 38 | Case series | *Very high* | Patients with AHA suffering from a severe bleed | Haemostatic response rate defined as either effective, partially effective or ineffective at 24 h and end of treatment  Safety | Yes |
| AHS Project | 65 | Case series | *Very high* | Patients with AHA | Incidence of AEs  Haemostatic response rate at 24 h and 72 h, defined as an excellent/good or fair/partially effective response | No |
| Porrazzo et al. (2021) | 26 | Case series | *Very high* | Patients with AHA | Haemostatic response rate based on Hb levels and/or resolution of bleeds  Thromboembolic events | No |
| **FEIBA** | | | | | | |
| EACH2 | 63 | Case series | *Very high* | Patients with AHA | Control of the primary bleeding episode  Safety | Yes |
| Porrazzo et al. (2021) | 19 | Case series | *Very high* | Patients with AHA | Haemostatic response rate based on Hb levels and/or resolution of bleeds  Safety | No |
| FAIR Registry | 56 | Case series | *Very high* | Patients with AHA | Dosage, duration of treatment, and efficacy  Safety | Yes |
| FEIBHAC Regsitry | 34 | Case series | *Very high* | Patients with AHA aged > 18 years with an initial or recurrent bleed and/or invasive procedure such as surgery | Overall assessment of haemostatic efficacy  Safety | Yes |
| Sallah et al. (2004) | 34 | Case series | *Very high* | Patients with AHA who were treated with FEIBA as first-line therapy | Major response to FEIBA defined as complete control or substantial reduction of bleeding  Safety | Yes |

AE = Adverse Events; AHA = Acquired Haemophilia A; Hb = Haemoglobin; SAE = Serious Adverse Events.

## 11. Comparative safety

The ADAR calculated the risk difference and relative risk using R (v.4.1.2) with the Meta package (v.4.20 2). An additional calculation was required for all-cause mortality for the Obizur vs. NovoSeven comparison. This was performed using the “epitab” command for cohort studies in STATA 15[[14]](#footnote-15).

### Treatment-related thrombosis

The aim of treatment for a bleed in patients with AHA is to increase clotting factor levels, so that haemostasis is achieved. A key adverse event which can result from the treatments is thrombosis (when a blood clot blocks a blood vessel). A marginal reduction of 4% risk of treatment-related thrombosis in favour of Obizur was found when compared to FEIBA. No difference in this outcome was detected between Obizur and NovoSeven (Table 5).

Treatment-related thrombosis is a key risk associated with AHA therapy and is of particular risk to patients who also have cardiovascular-related comorbidities. Pre-existing cardiovascular comorbidities ranged from 75.9 to 90.6% with the studies on Obizur treatment and was rarely reported in studies of the comparators. No prevalence rate is available for cardiovascular comorbidities in Australian patients with AHA. In the Australian context, Dix et al 2022 reported that 2 out of 29 (6.88% of cohort) Australian patients with AHA who had received at least one BPA reported a thromboembolic event. This is higher than the rate of treatment-related thrombosis observed in the case series.

Table 5 Naïve (indirect) comparison: Treatment-related thrombosis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Obizur  n/N (%)  k studies | NovoSeven  n/N (%)  k studies | FEIBA  n/N (%)  k studies | Obizur vs. NovoSeven  RD (95% CI), p-value  RR (95% CI), p-value | Obizur vs. FEIBA  RD (95% CI), p-value  RR (95% CI), p-value | GRADE |
| 1/129  (0.8%)  3 studies | 10/465  (2.2)  6 studies | 8/172  (4.7%)  4 studies | -0.01  [-0.03; 0.01]; p=0.1793  0.36  [0.05; 2.79]; p=0.3284 | -0.04  [-0.07; -0.00]; p=0.0296  0.17  [0.02; 1.32]; p=0.0892 | ⨁⨀⨀⨀  a,b,c |

a Very serious risk of bias due to all studies being uncontrolled

b Serious indirectness due to the evidence relying on indirect comparisons

c Serious risk of publication bias as results were mostly derived from observational studies

Abbreviations: CI = Confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RD = Risk Difference; RR = Relative Risk;

Source: Tables 42 and 76, pg 83 and 136 of the Commentary on MSAC 1714 ADAR

### Treatment-related Serious Adverse Events

Patients who received Obizur were 6% more likely to experience any treatment-related serious adverse event (SAE) in comparison to NovoSeven. No difference in treatment-related SAE incidence was detected between Obizur and FEIBA (Table 6).

Treatment-related SAEs often relate to thrombosis but can also include hypersensitivity and development/increase of inhibitor levels (anamnestic reaction). FEIBA has the additional risk of transmission of bloodborne pathogens as it is a blood-product, but the manufacturing process includes two dedicated and independent virus removal/inactivation steps to reduce this risk [[15]](#footnote-16). As per the FEIBA PI, there is an overall risk of adverse events of any severity occurring in >5% of all individuals exposed. There were no reported incidents of anamnestic reaction for NovoSeven or FEIBA. There were 3 instances reported for Obizur (2.3% of total patients). There were another 2 incidents in 2 patients reported for NovoSeven, however it was unclear whether these were associated with treatment.

Non-thrombotic treatment-related SAEs in the Australian population were not identified in Tay et al. 2012 or Dix et al. 2022.

Table 6 Naïve (indirect) comparison: Treatment-related SAEs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Obizur  n/N (%)  k studies | NovoSeven  n/N (%)  k studies | FEIBA  n/N (%)  k studies | Obizur vs. NovoSeven  RD (95% CI), p-value  RR (95% CI), p-value | Obizur vs. FEIBA  RD (95% CI), p-value  RR (95% CI), p-value | GRADE |
| 11/129  (8.5)  3 studies | 6/227  (2.6)  3 studies | 4/34  (11.8)  1 study | 0.06  [0.01; 0.11]; p=0.0281  3.23  [1.22; 8.52]; p=0.0181 | -0.03  [-0.15; 0.09]; p=0.5924  0.72  [0.25; 2.13]; p=0.5592 | ⨁⨀⨀⨀  a,b,c |

a Very serious risk of bias due to all studies being uncontrolled

b Serious indirectness due to the evidence relying on indirect comparisons

c Serious risk of publication bias as results were mostly derived from observational studies

Abbreviations: CI = Confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RD = Risk Difference; RR = Relative Risk;

Source: Tables 45 and 79, pg 98 and 138 of the Commentary on MSAC 1714 ADAR

### Treatment-related mortality

No difference was detected in treatment-related mortality between those patients receiving Obizur, compared to NovoSeven or FEIBA (Table 7).

However, the ADAR has not comprehensively reported whether there were any treatment related deaths in Study 241302 of Obizur. Of the 16 deaths that occurred during the trial, 5 deaths were related to AHA, and two were unknown. Further clarification is required.

There were no reports of treatment-related mortalities related to BPAs in Australian patients.

Table 7 Naïve (indirect) comparison: Treatment-related mortality

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Obizur  n/N (%)  k studies | NovoSeven  n/N (%)  k studies | FEIBA  n/N (%)  k studies | Obizur vs. NovoSeven  RD (95% CI), p-value  RR (95% CI), p-value | Obizur vs. FEIBA  RD (95% CI), p-value  RR (95% CI), p-value | GRADE |
| 0/79  (0%)  2 studies | 4/159  (2.52)  2 studies | 1/90  (1.11%)  2 studies | -0.03  [-0.06; 0.01]; p=0.1105  0.22  [0.01; 4.09]; p=0.3119 | -0.01  [-0.04; 0.02]; p=0.4872  0.38  [0.02; 9.18]; p=0.5511 | ⨁⨀⨀⨀  a,b,c |

a Very serious risk of bias due to all studies being uncontrolled

b Serious indirectness due to the evidence relying on indirect comparisons

c Serious risk of publication bias as results were mostly derived from observational studies

Abbreviations: CI = Confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RD = Risk Difference; RR = Relative Risk;

Source: Tables 48 and 82, pg 88 and 140 of the Commentary on MSAC 1714 ADAR

### All-cause mortality

The ADAR did not provide an indirect comparison of all-cause mortality for Obizur vs. NovoSeven. Instead, a survival analysis from a retrospective cohort series by Batt et al. 2022 was provided.

Batt et al. 2022 failed to find a difference in mortality hazard when comparing Obizur and NovoSeven, adjusting for age, sex and Charlson Comorbidity Index score (See Figure 5 in study). However, the use of Obizur resulted in a 45% reduction in the hazard of death compared to NovoSeven over the study period, which would be considered clinically important. The lack of statistical significance may be due to an underpowered study because when mortality was pooled with readmission, the hazard was significantly lower for Obizur. It is unclear whether a similar result will be seen in the Australian context as the authors postulate that Obizur tends to be available at healthcare centres with more facilities with superior clinicians. Naïve indirect comparisons of case series reported that patients who received Obizur were 14% more likely to die in comparison to NovoSeven and 10% more likely in comparison to FEIBA. When data from Batt et al. 2022 were combined with the case series data, no significant difference was detected between treatment arms overall (Table 8). This result should be interpreted with caution as they were unadjusted for underlying comorbidities and length of follow-up.

Table 8 Naïve (indirect) comparison: All-cause mortality

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Obizur**  **n/N (%)**  **k studies** | **NovoSeven**  **n/N (%)**  **k studies** | **FEIBA**  **n/N (%)**  **k studies** | **Obizur vs. NovoSeven**  **RD (95% CI), p-value**  **RR (95% CI), p-value** | **Obizur vs. FEIBA**  **RD (95% CI), p-value**  **RR (95% CI), p-value** | **GRADE** |
| 34/132  (25.8%)  3 studies | 45/377 (11.9%)  4 studies | 29/187  (15.5%)  4 studies | 0.14  (0.6, 0.22); p= 0.0002  2.2  (1.4, 3.2); p= 0.0002 | 0.10  [0.01; 0.19]; p=0.0271  1.66  [1.07; 2.59]; p=0.0246 | ⨁⨀⨀⨀  a,b,c |
| SA: Inclusion of Batt et al. 2022 | | | | | |
| 43/162 (26.5%)  4 studies | 108/513 (21%)  5 studies | NA | 0.05 (-0.02, 0.1);  p= 0.1438  1.26 (0.93, 1.7);  p= 0.1438 | NA |  |

a Very serious risk of bias due to all studies being uncontrolled

b Serious indirectness due to the evidence relying on indirect comparisons

c Serious risk of publication bias as results were mostly derived from observational studies

Abbreviations: CI = Confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RD = Risk Difference; RR = Relative Risk; SA: Sensitivity Analysis.

Source: Commentary Table 3 and Table 84, pg 91 and 141 of the Commentary on MSAC 1714 ADAR

In the Australian context, Dix et al. 2022 did not report any deaths whereas Tay 2012 reported 6 (25% of study cohort) deaths over a 12-year period. The rate of incidence of death is so low that a broad comparison is not useful.

The ADAR has not appropriately discussed how many of the deaths were due to treatment failure, which is also a measure of treatment efficacy. The evaluator identified that one patient who died of haemorrhage had received Obizur; one had received NovoSeven; and one had received FEIBA. Overall, it is unclear how many deaths were due to treatment failure, or whether they occurred as a result of a subsequent bleed.

### Clinical claim

The ADAR claimed the use of Obizur results in non-inferior safety compared with NovoSeven and FEIBA.

The evaluator disagreed with the methods used in the ADAR to establish non-inferiority in safety. This is discussed further in the clinical claim for Comparative effectiveness.

Overall, the evaluator considered Obizur is not consistently superior or inferior to NovoSeven in terms of safety. One of the key safety issues unique to Obizur is the fact that the treatment involves supplementation of a biomimetic form of FVIII. This means that there is increased potential for inhibitors for both human and porcine FVIII.

## 12. Comparative effectiveness

### Bleeding resolution

Across studies, bleed control or resolution was not appropriately described. It is unclear how transitive the reported efficacy outcomes are and whether they should be pooled. Therefore, the following estimate of effect has a very high risk of bias and should be interpreted with caution.

Patients who received Obizur were 8% less-likely to have their primary bleed resolve in comparison to those who received NovoSeven and 11% less-likely in comparison to those who received FEIBA (Table 9).

The ADAR claims that this result may be due to the fact that the studies of Obizur had more patients treated with second-line treatment and therefore, were more likely to be sicker, or fail treatment. When accounting for line of treatment in both comparisons, the direction of effect remained the same, however no significant difference was detected. It remains unclear whether line of treatment does negatively bias the efficacy of Obizur as this analysis is likely underpowered.

Table 9 Patients who had their primary bleed resolved

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Obizur  n/N (%)  k studies | NovoSeven  n/N (%)  k studies | FEIBA  n/N (%)  k studies | Obizur vs. NovoSeven  RD (95% CI), p-value  RR (95% CI), p-value | Obizur vs. FEIBA  RD (95% CI), p-value  RR (95% CI), p-value | GRADE |
| All lines | | | | | |
| 118/146  (80.8)  4 studies | 189/212  (89.2)  3 studies | 104/113  (92)  3 studies | -0.08  [-0.16; -0.01]; p=0.0325  0.91  [0.83; 0.99]; p=0.0365 | -0.11  [-0.19; -0.03]; p=0.0067  0.88  [0.80; 0.97]; p=0.0079 | ⨁⨀⨀⨀  a,b,d |
| First line only | | | | | |
| 66/75  (88)  4 studies | 189/212  (89.2)  3 studies | 102/111  (91.9) 3 studies | -0.01  [-0.10; 0.07]; p=0.7898  0.99  [0.90; 1.09]; p=0.7905 | -0.04  [-0.13; 0.05]; p=0.3934  0.96  [0.87; 1.06]; p=0.3972 | ⨁⨀⨀⨀  a,b,d |

⨁⨀⨀⨀ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a Very serious risk of bias due to all studies being uncontrolled

b Serious indirectness due to the evidence relying on indirect comparisons

d Serious risk of publication bias since the results were mostly derived from observational studies

Abbreviations: CI = Confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RD = Risk Difference; RR = Relative Risk

Source: Table 33 and Table 70, pg 75 and 133 of the Commentary on MSAC 1714 ADAR

Patients who received Obizur were 9% less likely to have their bleed resolve in comparison to those who received NovoSeven. When accounting for line of treatment in Obizur vs. NovoSeven, the direction of effect remained the same, however no significant difference was detected. No difference was detected in comparison to FEIBA (Table 10).

Table 10 Total number of bleeding episodes resolved

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Obizur  n/N (%)  k studies | NovoSeven  n/N (%)  k studies | FEIBA  n/N (%)  k studies | Obizur vs. NovoSeven  RD (95% CI), p-value  RR (95% CI), p-value | Obizur vs. FEIBA  RD (95% CI), p-value  RR (95% CI), p-value | GRADE |
| All lines | | | | | |
| 101/128  (78.9)  2 studies | 452/515  (87.8)  3 studies | 44/50  (88)  1 study | -0.09  [-0.16; -0.01]; p=0.0225 0.90  [0.82; 0.99]; p=0.0284 | -0.09  [-0.21; 0.02]; p=0.1195  0.90  [0.78; 1.03]; p=0.1160 | ⨁⨀⨀⨀  a,b,d |
| First line | | | | | |
| 64/76  (84.2)  2 studies | 399/443  (90.1)  3 studies | Not available | -0.06  [-0.15; 0.03]; p=0.1849  0.93  [0.84; 1.04]; p=0.1970 | Not available | ⨁⨀⨀⨀  a,b,d |
| Subsequent lines | | | | | |
| 37/52  (71.2)  2 studies | 53/72  (73.6)  3 studies | Not available | -0.02  [-0.18; 0.14]; p=0.7631  0.97  [0.77; 1.21]; p=0.7639 | Not available | ⨁⨀⨀⨀  a,b,d |

⨁⨀⨀⨀ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a Very serious risk of bias due to all studies being uncontrolled

b Serious indirectness due to the evidence relying on indirect comparisons

d Serious risk of publication bias since the results were mostly derived from observational studies

Abbreviations: CI = Confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RD = Risk Difference; RR = Relative Risk

Source: Table 35 and Table 73, pg 77 and 134 of the Commentary on MSAC 1714 ADAR

### Positive rate at 24 hours of treatment

No difference was detected between Obizur and NovoSeven in terms of a positive response rate at 24 hours (Table 11).

This comparison is highly uncertain as the study of Obizur relied on FVIII activity whereas the studies of NovoSeven relied on clinical judgement. This is because Obizur requires monitoring of FVIII activity throughout the treatment period, whereas this typically does not occur with NovoSeven. This may bias the outcome in favour of Obizur as FVIII activity may show a positive response quicker than a clinically recognisable response.

Table 11 Naïve (indirect) comparison: Positive response rate at 24 h

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Obizur  n/N (%)  k studies | NovoSeven  n/N (%)  k studies | RD [95% CI];  p value | RR [95% CI];  p value | Quality of evidence (GRADE) |
| 28/28  (100)  1 study | 65/70  (92.9)  2 studies | 0.07  [-0.01; 0.15]; p=0.0733 | 1.08  [1.01; 1.15]; p=0.0254 | ⨁⨀⨀⨀  a,b,c,d |

For the purposes of this submission, the Risk difference and Relative Risk were calculated using R (v.4.1.2) with the Meta package (v.4.20‑2)

⨁⨀⨀⨀ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a Very serious risk of bias due to all studies being uncontrolled

b Serious indirectness due to the evidence relying on indirect comparisons

c Serious imprecision since the total number of events did not exceed 200

d Serious risk of publication bias as results were mostly derived from observational studies

Abbreviations: CI = Confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RD = Risk Difference; RR = Relative Risk

Source: Table 3, pg 81 of the Commentary on MSAC 1714 ADAR

### Clinical claim

The ADAR claimed that use of Obizur results in non-inferior effectiveness compared with NovoSeven and FEIBA.

The ADAR has assumed a non-significant difference in effectiveness between Obizur and NovoSeven or FEIBA as a signal of non-inferiority. This may not be reasonable, as a lack of statistically significant differences is not necessarily evidence of no difference between groups, as the studies may not have been sufficiently powered to detect a difference or it may be due to other confounding factors.

The body of evidence across all treatments is comprised of small, non-comparative studies subject to a high degree of bias, and the comparison is naïve with no adjustment for confounders. However, with AHA being a very rare disease this may be the best available evidence as further data may be unlikely to be available in future.

There were particular issues with regard to reporting of efficacy outcomes across studies. Many studies did not report how bleeding control/resolution was measured. Additionally, there was little description of the time-to-resolution/control. This has financial implications on the cost of monitoring and length of stay in hospital, particularly the former as Obizur requires additional tests to monitor response.

The ADAR used a naïve comparison when comparing across studies of Obizur to justify an initial dose lower than what is recommended in the PI (200 U/kg). The evaluator considered the ADAR did not provide sufficient clinical evidence to support this lower initial dose and that a comparison based on a pharmacokinetics study or other comparative studies would have presented a stronger basis for utilising a lower initial dose. The evaluator also considered that this has the potential to significantly impact the economic evaluation of Obizur with regard to the estimated equi-effective doses, monitoring costs and length of stay in hospital for the patient.

Overall, the evaluator considered the evidence provided in the ADAR was insufficient to support a claim of non-inferior efficacy and safety to NovoSeven and FEIBA.

## 13. Economic evaluation

The ADAR adopted a cost-minimisation approach (CMA). Two CMAs were presented for each comparator separately, and then the proposed price per vial of Obizur was derived by weighting the respective cost-minimised prices by the observed distribution of use of each comparator (NovoSeven and FEIBA). The presentation of a CMA may only be reasonable if MSAC accept the clinical claims of non-inferiority.

The CMA considered the cost of medicines and additional costs (offsets) resulting from differences in treatment-specific monitoring and the management of thrombotic events. The prices for NovoSeven and FEIBA were taken from the NPPL (1 July 2022). The CMA assumed no differences in prescribing or administration profiles between Obizur and either BPA. However, there may be differences in the duration of Obizur and BPA treatment, where Obizur may have a longer duration of treatment compared to NovoSeven (and shorter duration relative to FEIBA). As patients are required to remain in hospital until the acute bleeding episode is resolved, costs associated with differences in the duration of in-hospital stay may impact the price per vial of Obizur. However, the impact of differences in duration of treatment could not be tested during the evaluation as there is no specific Australian refined diagnosis-related groups (AR-DRG) code for haemophilia admissions. The cost of monitoring and management of thrombotic events was informed by MBS and AR-DRGs, respectively.

The equi-effective doses for Obizur and each BPA were derived from the average total dose administered for an acute bleeding episode per patient weighted across the respective clinical studies. The equi-effective doses for Obizur and each BPA proposed in ADAR are presented in Table 12.

Table 12 Equi-effective doses: Obizur versus NovoSeven and FEIBA estimated in ADAR

|  |
| --- |
| Obizur [REDACTED] Units per episode ≡ NovoSeven [REDACTED] µg per episode  Obizur [REDACTED] Units per episode ≡ FEIBA [REDACTED] Units per episode |

Source: Table 93, pg 143 and Table 104, pg 158 of the MSAC 1714 ADAR

### Uncertainties and errors in estimation of equi-effective doses

#### Evidence base

There is substantial variation in baseline patient characteristics such as site of the bleed, bleed severity and the proportion of patients undergoing prior lines of therapy in the included studies – both within a treatment (e.g., Obizur studies) and across treatments (e.g., Obizur vs NovoSeven studies). The ADAR established the equi-effective doses without adjusting for differences in baseline patient characteristics which is likely to affect respective doses per patient. Therefore, the equi-effective doses based on the studies included in the unadjusted naïve indirect comparisons are highly uncertain.

#### Dose of Obizur

The Obizur PI recommends a starting dose of 200 U/kg administered intravenously, with dose adjustments every 4 to 12 hours based on clinical response and coagulant factor VIII (FVIII). The PI also suggests that initial dosing below the recommended 200 U/kg has been associated with lack of efficacy. Of the included Obizur studies, 3 out of 4 initiated Obizur at a dose of approximately 100 U/kg for most patients. The dose of Obizur would increase to [REDACTED] units per episode if studies using loading doses consistent with the PI are used to derive the equi-effective dose.

#### Dose of NovoSeven

The ADAR considered Obizur dosing based only on episodes where bleeds were resolved. For NovoSeven, it is not clear if the dosing was based on those bleeding episodes which were resolved or if all treated bleeding episodes regardless of resolution of the bleed were considered. Dosing regardless of bleed resolution was used in at least one included study[[16]](#footnote-17). This inconsistency in approach to derive equi-effective doses is not reasonable.

One included study, Hay et al. 1997[[17]](#footnote-18), reported an unusually high (153) number of infusions which are unlikely in current clinical practice. The dose per infusion (104.2 µg/kg) reported in another study (Hay et al. 2017[[18]](#footnote-19)) was only for initial dose. Therefore, the use of dosing information from these studies is uncertain. During the evaluation, equi-effective doses of NovoSeven excluding these studies and including information from a study excluded by the ADAR(Borg et al. 2013[[19]](#footnote-20)) reduced the equi-effective dose of NovoSeven from [REDACTED to [REDACTED] µg per episode.

#### Dose of FEIBA

The ADAR excluded mean duration of treatment from Borg et al. 2015[[20]](#footnote-21) (4.73 days; derived from median and IQR) in the calculations and assumed initial doses per infusion for average doses per infusion from Borg et al. 2015 and Baudo et al. 2012[[21]](#footnote-22) which is inappropriate. The ADAR also incorrectly calculated infusions per day[[22]](#footnote-23). During the evaluation, including the mean duration of treatment from Borg et al. 2015, correcting for error in calculation of infusions per day and estimating dose per infusion from Borg et al. 2015 and Baudo et al. 2012 resulted in a reduced dose of FEIBA per episode from [REDACTED] Units to [REDACTED] Units.

#### Body weight

Weighted average body weight (73.1 kg) was derived based on 5 studies (OBI-1-301, Study 241302, Baudo et al. 2012, Borg et al. 2013 and ACQUI-7). Mean body weight of patients included in these studies ranged from 63.62 kg to 73.40 kg. None of the studies included Australian population and it is uncertain if the weighted average body weight was representative of Australian population with AHA.

Table 13 Equi-effective doses: Obizur versus NovoSeven and FEIBA estimated during the commentary

|  |
| --- |
| Obizur REDACTED Units per episode ≡ NovoSeven REDACTED µg per episode  Obizur REDACTED Units per episode ≡ FEIBA REDACTED Units per episode |

Source: Commentary Table 5, pg 161 and Commentary Table 7, pg 183 of the Commentary on MSAC 1714 ADAR

Table 14 Economic evaluation: Obizur versus NovoSeven

|  | **Obizur** | **NovoSeven** | | | | **Incremental** |
| --- | --- | --- | --- | --- | --- | --- |
| **500** | **1 mg** | **2 mg** | **5 mg** | **8 mg** |
| **Medicines** | | | | | | |
| Vials per episode | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |  |
| Price per vial per episode | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| Cost of vials per episode | $REDACTED | $REDACTED | | | |
| Total | $REDACTED | $REDACTED | | | | -$573.58 |
| **Monitoring** | | | | | | |
| FVIII activity | $REDACTED | $REDACTED | | | |  |
| Inhibitor titres | $REDACTED | $REDACTED | | | |
| Total | $REDACTED | $REDACTED | | | | $629.47 |
| **Adverse events** | | | | | | |
| Thrombotic events | $REDACTED | $REDACTED | | | |  |
| Total | $REDACTED | $REDACTED | | | | -$55.89 |
| **Total cost of treatment per bleeding episode** | | | | | | |
| Total | $REDACTED | $REDACTED | | | | $0.00 |

Source: Table 98, pg 148 of the MSAC 1714 ADAR

Table 15 Economic evaluation: Obizur versus FEIBA

|  | **Obizur** | **FEIBA** | | | **Incremental** |
| --- | --- | --- | --- | --- | --- |
| **500** | **500 Units** | **1,000 Units** | **2,500 Units** |
| **Medicines** | | | | | |
| Vials per episode | REDACTED | REDACTED | REDACTED | REDACTED |  |
| Price per vial | REDACTED | $1,200 | $2,400 | $6,000 |  |
| Cost of vials per episode | $REDACTED | $REDACTED | $REDACTED | $REDACTED |  |
| Total | $REDACTED | $REDACTED | | | -$414.33 |
| **Monitoring** | | | | | |
| FVIII activity | $REDACTED | $REDACTED | | |  |
| Inhibitor titres | $REDACTED | $REDACTED | | |  |
| Total | $REDACTED | $REDACTED | | | $571.85 |
| **Adverse events** | | | | | |
| Thrombotic events | $REDACTED | $REDACTED | | |  |
| Total | $REDACTED | $REDACTED | | | -$157.52 |
| **Total cost of treatment per bleeding episode** | | | | | |
| Total | $REDACTED | $REDACTED | | | $0.00 |

Source: Table 110, pg 164 of the MSAC 1714 ADAR

The ADAR proposed a confidential price of $[REDACTED] for Obizur 500 U vial by weighing the cost per vial that resulted from the CMAs versus NovoSeven ($[REDACTED]) and FEIBA ($[REDACTED]) with the current market share of NovoSeven (78%) and FEIBA (22%). Applying the 1 January 2023 NPPL updated prices of NovoSeven and FEIBA results in a lower cost-minimised price of $[REDACTED] (versus NovoSeven ($[REDACTED]) and FEIBA ($[REDACTED])). Information on the current market share of NovoSeven and FEIBA were based on utilisation as reported in the ABDR Annual report (2019-2020). A total of seven patients received treatment with NovoSeven and less than five patients received treatment with FEIBA. As exact numbers of patients receiving treatment with FEIBA is unclear, the ADAR assumed that two patients were treated with FEIBA. Therefore, changes in the number of patients treated with FEIBA will affect market share estimates and thus the price per vial of Obizur.

### Sensitivity Analyses

The results of key sensitivity analyses performed during the evaluation are presented below.

Table 16 Results of the sensitivity analyses performed during the evaluation – Obizur versus NovoSeven

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Dose per episode – Obizur (U)** | **Dose per episode – NovoSeven (µg)** | **Cost-minimised price per vial for Obizur** | **Change in price per vial** |
| **Base case** | REDACTED | REDACTED | $REDACTED | \_ |
| **Sensitivity analyses** |  |  |  |  |
| **A.** Initial dose of Obizur – included studies only with 200 U/kg initial dosing | REDACTED | REDACTED | $REDACTED | -49% |
| **B.** Exclusion of studies Hay et al. 1997 and Hay et al. 2017 | REDACTED | REDACTED | $REDACTED | -58% |
| **C. Using updated NovoSeven pricesa** | REDACTED | REDACTED | $REDACTED | -8% |
| **A + B** | REDACTED | REDACTED | $REDACTED | -79% |
| **A+B+C** | REDACTED | REDACTED | $REDACTED | -80% |

Source: Commentary Table 6, pg 170 of the Commentary on MSAC 1714 ADAR

a Prices of NovoSeven updated at 01 January 2023

Table 17 Results of the sensitivity analyses performed during the evaluation – Obizur versus FEIBA

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Dose per episode – Obizur (U)** | **Dose per episode – FEIBA (U)** | **Cost-minimised price per vial for Obizur** | **Change in price per vial** |
| **Base case** | REDACTED | REDACTED | $REDACTED | \_ |
| **Sensitivity analyses** |  |  |  |  |
| **A.** Initial dose of Obizur – included studies only with 200 U/kg initial dosing | REDACTED | REDACTED | $REDACTED | -49% |
| **B.** Revised dose of FEIBA | REDACTED | REDACTED | $REDACTED | -23% |
| **Using updated FEIBA pricesa** | REDACTED | REDACTED | $REDACTED | -5% |
| **A + B** | REDACTED | REDACTED | $REDACTED | -61% |
| **A+B+C** | REDACTED | REDACTED | $REDACTED | -63% |

Source: Commentary Table 8, pg 190 of the Commentary on MSAC 1714 ADAR

a Prices of FEIBA updated at 01 January 2023

## 14. Financial/budgetary impacts

An epidemiological approach was used to estimate the total number of patients with AHA who receive treatment for acute bleeding episodes. The total number of patients who are treated for a bleeding episode was extrapolated from the ABDR Annual report (2019-2020). Also derived from this source was the proportion of patients who received treatment with a BPA (75%). Of the 75% treated with a BPA, market share estimates of NovoSeven (78%) and FEIBA (22%) were based on observed utilisation (as reported in the ABDR Annual report 2019-2020). Given small numbers of patients treated with FEIBA, the number of patients receiving FEIBA was assumed. Uncertainty with this approach has been described in Section 11.

The base case analysis applied a bleeding rate of 4.68 per year as reported in Holstein et al. (2020) to estimate the number of bleeding episodes per patient treated each year. The estimated bleeding rate, as derived from the literature is uncertain. If the dose per bleed derived from Section 3 of the ADAR is considered, the number of bleeds per year is inconsistent with thedispensed amounts of BPAs from the ABDR. Based on the ADAR estimated dose per bleed and average annual dispensed dose from the ABDR for NovoSeven and FEIBA, the number of bleeds per year was estimated to be [REDACTED][[23]](#footnote-24) and [REDACTED][[24]](#footnote-25) respectively.

Alternatively, the number of bleeds per year used in the base case may be accurate and the dose per bleed may be inaccurate. Using the ADAR’s approach to estimating the total dose of BPAs used, applied to the ABDR data for actual dispensed amounts, the ADAR predicts more than double the amount of NovoSeven, and 4 times the amount of FEIBA than was actually dispensed (Table 18). This suggests that the average dose per bleed and/or the number of bleeds per year has been overestimated. Dose per bleed estimated during the commentary (Table 13) also suggested the ADAR might have overestimated the dose per bleed for NovoSeven and FEIBA. While the uncertainty in the estimation of bleeds per patient per year had only a minor impact on net financial estimates (Scenario 2, Table 19), uncertainty in the estimation of the dose per bleed resulted in a substantial increase in the net costs (Scenario 3, Table 19).

Table 18 Discrepancy between the annual dispensed dose of NovoSeven and FEIBA, and that predicted in the ADAR based on the proposed dose per bleed and the number of bleeds per year

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Step | Description | NovoSeven | FEIBA | Calculations |
| #1 | Treated | 7 | 2 | ABDR report |
| #2 | Annual dispensed dose | 2,556,000 (ug) | 196,000 (U) | ABDR report |
| #3 | Mean annual dose per patient | 365,143 (ug) | 98,000 (U) | = #2 / #1 |
| #4 | Bleeds/patient in ADAR | 4.68 | 4.68 | Holstein 2020 |
| #5 | Dose/bleed in ADAR | REDACTED (ug) | REDACTED (U) | Table 12 |
| #6 | Dose/bleed estimated during commentary | REDACTED (ug) | REDACTED (U) | Table 6 |
| #7 | Mean dose per bleed to match proposed bleeds per year | REDACTED (ug) | REDACTED (U) | = #3 / #4 |
| #8 | Mean bleeding episodes per year to match proposed dose | REDACTED | REDACTED | = #3 / #5 |
| #9 | Annual dispensed dose using approach in the ADAR | REDACTED ug (211% of actual dispensed) | REDACTED U (401% of actual dispensed) | = #1 x #4 x #5 |

Source: Commentary Table 12, pg 203 of the Commentary on MSAC 1714 ADAR

The effect of uncertainty on the financial impact in terms of number of bleeds per patient per year and doses per bleed has been tested during the evaluation (Table 19). Forecasting the utilisation of Obizur using the dispensed quantities of FEIBA and NovoSeven as reported by the ABDR (Table 19, Scenario 2) results in an estimate that is roughly 42% of the estimate presented in the ADAR. The net cost of BPAs estimated using actual dispensed data from the ABDR annual report (between $0 and <$10 million in 2023) is substantially lower than would be predicted using the variables from the ADAR (between $10 million and $20 million). However, the net impact of listing Obizur is minor as it is accompanied by an equivalent change in the use of FEIBA and NovoSeven.

Estimating the impact while retaining the ADAR’s assumption of bleeds per patient per year (4.68) but applying the revised dose per bleed estimates (Table 19, Scenario 3) resulted in a substantial increase in the net cost to the NBA which is due to the reduction in the estimated dose per bleed of BPAs accompanied by an increase in the dose of Obizur.

The ADAR assumed an uptake rate of [REDACTED]% in Year 1 for Obizur increasing to [REDACTED]% from Year 3 to Year 6. The proposed uptake rate is uncertain as no justification was provided to support the low uptake rates assumed in the first two years of listing. Given the advantages of Obizur in terms of FVIII activity monitoring and lower risk of thrombosis, the uptake rate assumed may be an underestimate in these years. However, as Obizur, FEIBA and NovoSeven are proposed to be interchangeable, the evaluator considered changing the uptake rate will not have an impact on the net cost to the NBA assuming equi-effective dosing is correct.

A weighted average cost per vial (500 U) of $[REDACTED] for Obizur estimated from the CMAs versus NovoSeven ($[REDACTED]) and FEIBA ($[REDACTED]) with the current market share of 78%/22% for NovoSeven and FEIBA as weights was used to estimate the financial impact in the ADAR (and is represented in Table 19 below).

MSAC Executive suggested that an estimation of cost-offsets due to the substitution of treatment with BPAs should also form part of the financial analyses (MSAC Executive minutes, April 2022). The financial analysis included cost-offsets due to a reduction in use of BPAs. In addition, the ADAR included cost-offsets to hospital budgets due to the reduction in cost of managing treatment-related AEs (thrombotic events). However, the ADAR did not include additional costs/cost-offsets due to differences in the duration of treatments for bleeds. It is uncertain that listing Obizur would result in cost savings to hospital budgets given patients would likely remain in hospital for the duration of treatment, where the average duration of treatment with Obizur ([REDACTED] days) is longer than NovoSeven ([REDACTED] days) but shorter than FEIBA ([REDACTED] days).

**Table 19 Financial implications for the National Blood Agreement**

|  | **2023** | **2024** | **2025** | **2026** | **2027** | **2028** |
| --- | --- | --- | --- | --- | --- | --- |
| People diagnosed with AHA | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| People receiving treatment for AHA | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| People receiving BPAs | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| **Scenario 1: Utilisation and impact of BPAs and Obizur based on ADAR assumptions of [REDACTED] bleeds per patient, and [REDACTED] U FEIBA, [REDACTED] ug NovoSeven and [REDACTED] U Obizur per bleed (ADAR base case)** | | | | | | |
| **Without Obizur** | | | | | | |
| Amount of FEIBA dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of NovoSeven dispensed (ug ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Total cost to NBA before Obizur (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| Total cost to NBA before Obizura (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| **With Obizur** | | | | | | |
| Amount of FEIBA dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of NovoSeven dispensed (ug ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of Obizur dispensed (Units ‘000) | REACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Total cost to NBA after Obizur (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| Total cost to NBA after Obizura (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| **Net cost to NBA (‘000)** | **$13** | **$19** | **$23** | **$25** | **$25** | **$27** |
| **Net cost to NBAa (‘000)** | **$11** | **$16** | **$19** | **$21** | **$21** | **$23** |
| **Scenario 2: Utilisation and impact of BPAs and Obizur based on quantities forecasted from the dispensed amounts in the ABDR 2019-2020 annual report** | | | | | | |
| **Without Obizur** | | | | | | |
| Amount of FEIBA dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of NovoSeven dispensed (ug ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Total cost to NBA before Obizur (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| Total cost to NBA before Obizura (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| **With Obizur** | | | | | | |
| Amount of FEIBA dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of NovoSeven dispensed (ug ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of Obizur dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Total cost to NBA after Obizur (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| Total cost to NBA after Obizura (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| **Net cost to NBA (‘000)** | **-$18** | **-$26** | **-$32** | **-$35** | **-$34** | **-$37** |
| **Net cost to NBAa (‘000)** | **-$12** | **-$17** | **-$20** | **-$22** | **-$22** | **-$24** |
| **Scenario 3: Utilisation and impact of BPAs and Obizur based on ADAR assumption of [REDACTED] bleeds per patient, and dose per bleed estimated in the commentary [REDACTED] U FEIBA, [REDACTED] ug NovoSeven and [REDACTED] U Obizur per bleed** | | | | | | |
| **Without Obizur** |  |  |  |  |  |  |
| Amount of FEIBA dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of NovoSeven dispensed (ug ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Total cost to NBA before Obizur (‘000) | **$REDACTED** | **$REDACTED** | **$REDACTED** | **$REDACTED** | **$REDACTED** | **$REDACTED** |
| Total cost to NBA before Obizura (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| **With Obizur** |  |  |  |  |  |  |
| Amount of FEIBA dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of NovoSeven dispensed (ug ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Amount of Obizur dispensed (Units ‘000) | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Total cost to NBA after Obizur (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| Total cost to NBA after Obizura (‘000) | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED | $REDACTED |
| **Net cost to NBA (‘000)** | **$9,118** | **$13,127** | **$16,043** | **$17,610** | **$17,496** | **$19,063** |
| **Net cost to NBAa (‘000)** | **$8,472** | **$12,196** | **$14,905** | **$16,361** | **$16,255** | **$17,711** |

Source: Commentary Table 14, pg 217 of the Commentary on MSAC 1714 ADAR

a Using updated prices of NovoSeven and FEIBA at 01 January 2023

## 15. Other relevant information

Nil.

## 16. Key issues from ESC to MSAC

|  |
| --- |
| **Main issues for MSAC consideration**  **Clinical issues:**   * Acquired Haemophilia A (AHA) is an extremely rare condition affecting approximately 100 individuals in Australia, of whom 10-20 receive treatment in a given year. There is substantial variability in severity of bleeding, which is confounded by age and aetiology, that impairs the generalisability of clinical outcomes reported in trials and registry studies. * Due to the rarity of AHA, there are limited clinical trial data available, and it is unlikely that randomised controlled trials will be forthcoming. The Australian Bleeding Disorders Registry (ABDR) should be able to capture data on Obizur product use and clinical outcomes. * The clinical effectiveness and safety of Obizur appears to be non-inferior compared with each of the two comparators (as monotherapy). The claims of non-inferiority are the basis for the cost-minimisation analysis against each comparator. However, these claims are based on limited evidence and are uncertain. * The proposed initial dose (between 100-200 Units/kg) for treatment with Obizur is lower than currently recommended in the product information (PI) (200 Units/kg). The initial dose of Obizur differed across the studies and some used an initial dose below 200 Units/kg. This may be appropriate, but in the absence of any national guidelines for management of AHA, further advice from professional societies could be sought. * AHA requires management in specialist centres, and there may be availability issues for patients presenting with bleeding outside of these settings, who may need urgent therapy.   **Economic issues:**   * If the claims of non-inferiority are not accepted, then there is no basis on which to rely on the weighted cost-minimised approach to inform public funding arrangements. * Many confounding factors contribute to the uncertainty in the equi-effective dose calculations. Some are inherent due to disease rarity (and hence the lack of controlled trials) and cannot be directly addressed or mitigated. However, the numerical approach to calculating the equi-effective doses is unnecessarily convoluted and appears to favour Obizur. * A cost-effective price has not been established for BPAs listed on the National Product Price List (NPPL). Therefore, even if Obizur is cost-minimised to the comparator prices, there is limited confidence that the comparator prices are cost-effective prices. Whilst it is recognised that the paucity of evidence makes it difficult to calculate an ICER for Obizur versus either of the comparator agents, it may instead be informative to calculate the average cost per (resolved) bleed for each agent, and then compare these values. * Noting clinician advice that starting doses less than 200 Units/kg are used in clinical practice, the studies that were excluded from the Commentary sensitivity analyses on the basis of a starting dose less than 200 Units/kg should be included in the base case analysis. * While the clinical reasoning for giving no intervention in practice is understandable, the ADAR did not include a comparison for Obizur versus no intervention in the economic evaluation * The impact of the observed difference in length of stay according to individual therapy has not been completely accounted for in the weighted cost-minimisation approach: the hospital costs for different lengths of stay need to be incorporated (not just the differences in number of infusions based on assumptions around infusions per day). * It was noted that there may be patients who receive more than one therapy, but this is not accounted for in the cost-minimisation approach.   **Financial issues:**   * There is significant uncertainty regarding the total likely cost of Obizur and the net financial impact due to the uncertainties with the economic evaluation and the low patient numbers. The low net financial impact claimed in the ADAR is only possible if the equi-effective dose calculations are reliable.   **Other relevant information:**   * If recommended for public funding, a post-implementation utilisation review should determine the average dose per patient per bleed (all bleeds, resolved and unresolved) in practice for Obizur, NovoSeven and FEIBA, or combinations thereof. * **If a risk-sharing arrangement between the National Blood Authority and Obizur supplier is to be implemented, it should consider price reductions to address the risk of the average dose per patient per bleed being higher in practice than assumed in the ADAR.** |

**ESC discussion**

ESC noted that this application from Takeda Pharmaceuticals Australia requested Obizur® (susoctocog alfa) to be publicly funded under the National Blood Agreement (the Agreement) through the National Product Price List (NPPL) for the treatment of bleeding episodes in adult patients with acquired haemophilia A (AHA). Therefore, ESC noted that an MBS item descriptor was not applicable for this application. ESC noted that the National Blood Authority (NBA) initially conducted a Cycle 1 multi-criteria analysis (MCA) evaluation on this application in 2020 but concluded that a referral to MSAC was needed to address:

* uncertainty remaining on whether Obizur offers incremental health outcomes or safety benefits compared to bypassing agents (BPAs)
* uncertainty on whether there will be cost savings or additional costs.

ESC noted that the nominated comparators were BPAs; NovoSeven® RT and FEIBA NF®. ESC noted BPAs are on the NPPL but are not solely for the treatment of patients with AHA. ESC noted there is no ability to monitor treatment response in patients given BPAs alone, and repeated dosing is based on clinical response and experience. In contrast, the effectiveness of treatment with Obizur can be monitored using FVIII levels and activated partial thromboplastin time (MBS item 65120).

ESC considered there to be a clinical need for access to improved therapies that also improve the ability to monitor treatment response during a bleeding episode in patients with AHA. ESC noted AHA is a very rare disease which often has a sudden onset, has numerous underlying or associated conditions, a highly variable presentation and clinical course, and can result in limb-threatening and life-threatening bleeding. ESC noted due to the rarity of AHA, the evidence base is limited and the numbers of patients with AHA treated in Australia each year for a bleeding episode is unclear. ESC also noted that AHA requires management in specialist centres (by experienced haematologists, and in some cases in Haemophilia Treatment Centres (HTC)), and access for patients outside these settings or in emergency situations is unclear.

ESC noted the UK-based National Health Service have a Policy on Obizur treatment for a bleeding episode in people with AHA[[25]](#footnote-26) which contains a clinical management algorithm for specialist centres (see figure 2). ESC considered that this algorithm could be adapted for use in Australia in the absence of national guidelines. ESC noted that the most appropriate line of therapy for Obizur, relative to existing therapies, was not categorically defined. ESC also noted that the management of Obizur non-responders was unclear, and in practice patients may require more than one therapy. ESC considered that haematologists should be the sole prescriber for Obizur.

ESC noted the evidence base was low-quality with a high risk of bias. ESC noted the application included 16 case series and one retrospective cohort study comparing Obizur and NovoSeven. ESC noted that there were many differences between the studies such as patient characteristics (i.e., age, comorbidities (e.g., pre-existing cardiovascular disease)), when Obizur was used (the line of therapy), the duration of follow-up (maximum of 180 days) and how the analysis was conducted. All studies had small patient numbers (which ESC considered reasonable, given the rarity of AHA). ESC noted there are no prospective randomised controlled trials directly comparing Obizur with any BPA, and it is unlikely there will be any forthcoming. ESC noted that data on the use of Obizur in pregnant and lactating women or its effect on fertility is unavailable, and data on use in patients less than 18 years of age is insufficient.

ESC considered the clinical effectiveness and safety of Obizur appears to be non-inferior compared with each comparator, however, this is based on limited evidence and is uncertain.

ESC noted that the applicant-developed assessment report (ADAR) proposed an initial dose between 100 and 200 Units (U)/kg. However, ESC noted that international guidelines[[26]](#footnote-27) and the Product Information (PI) for Obizur recommend an initial dose of 200 U/kg. ESC noted the pre-ESC response included a survey of two clinicians and noted an Australian case series of four patients[[27]](#footnote-28) that used an initial dose of 100–120 U/kg to justify the lower dose being used in current practice. [REDACTED]. Based on the evidence presented, ESC considered that an initial dose between 100 and 200 U/kg may be appropriate, relative to the clinical judgement of the treating practitioner and individual patient circumstance (including assessment of laboratory results).

ESC noted that, based on the naïve indirect comparisons, the rates of treatment-related serious adverse events (SAEs) and death appear to be low with Obizur, but that treatment-related SAEs are 6% more likely with Obizur compared to NovoSeven. ESC considered that it was difficult to fully quantify the comparisons for treatment-related thromboembolic events due to differences in patient characteristics across trials and the unknown presence of pre-existing cardiac comorbidities in patients with AHA.

Regarding comparative effectiveness, ESC noted that resolution of the primary bleeding episodes was similar between Obizur and the comparators when used as first-line treatment, but less likely for Obizur when used as any line of treatment. ESC noted that the ADAR claimed this was due to more studies using Obizur as second-line treatment, so patients were likely to be more severely ill. It was reported that naïve indirect comparisons with pooled NovoSeven data found that Obizur results in fewer total resolved bleeding episodes but has a similar positive response rate at 24 hours. However, bleed control or resolution was not appropriately described across studies, and the outcome of ‘unresolved bleeds’ is not comprehensively described in the studies (or well defined in clinical practice) to determine effectiveness outcomes for all patients.

ESC also noted the need for testing anti-porcine antibodies prior to treatment with Obizur, and that patients with neutralising anti-porcine antibodies did respond to treatment, and the presence of antibodies did not affect the response rate at 24 hours. However, these patients did require higher doses than patients without antibodies, and patients with titre of inhibitors >20 Bethesda Units were excluded from the registration trial. ESC noted the clinical advice that when a patient presents with a life or limb-threatening bleed, treatment may need to commence prior to the result of the anti-porcine antibody titre being available.

ESC noted that consultation feedback was received from the Haematology Society of Australia and New Zealand (HSANZ), which was strongly supportive of listing, considering Obizur to be non-inferior relative to comparators in providing haemostatic control. HSANZ also highlighted that Obizur offers more personalised therapy for a group of patients who often have critical bleeding and high mortality. ESC considered that further feedback should be sought from professional societies regarding input on what would be considered an appropriate initial dose and where Obizur would be used in the line of therapy in the absence of national guidelines. ESC considered that bodies such as the Thrombosis and Haemostasis Society of Australia and New Zealand, the Australian Haemophilia Centre Directors’ Organisation (AHCDO) and Haemophilia Foundation Australia (HFA) should be sought for further input. ESC considered that further consumer feedback would be informative on whether consumers would have concerns with the SAEs, which appear higher for Obizur than for NovoSeven, based on limited information available.

ESC noted that the ADAR’s economic evaluation used a cost-minimisation approach (CMA) presented for each comparator separately. The proposed price per vial of Obizur was based on the weighted average of equi-effective doses and market share data of each comparator. ESC considered there were issues with the assumptions used to calculate the equi-effective doses and noted the cost-effectiveness of BPAs has not been established.

ESC noted the ADAR did not include an economic comparison for Obizur versus no intervention. ESC accepted the clinical reasoning for not including this analysis since there is a lack of contemporary data of the natural progression of a bleeding episode with no treatment. However, ESC noted that without BPAs having an established cost-effective price, there is limited confidence that the cost-minimised price of Obizur to BPAs can be assumed to be cost-effective. ESC recalled that MSAC previously rejected emicizumab for congenital HA (MSAC Application 1510[[28]](#footnote-29)) and had requested that “the cost-effectiveness of current practice be determined as a means to then determine the cost-effectiveness of emicizumab in the proposed population.”

ESC considered the equi-effective doses to be uncertain and noted that it only holds if the claim of non-inferiority is accepted. ESC noted that the pre-ESC response revised the equi-effective dose calculations to account for differences in treatment duration for Obizur and the two BPAs. ESC calculated that this would result in a revised weighted cost-minimised Obizur price per vial of $[REDACTED]. ESC noted that the most extreme sensitivity analyses from the commentary decreased the weighted price per vial of Obizur to $[REDACTED]. However, these analyses excluded studies using an initial dose less than 200 U/kg, which ESC considered may not be reasonable if a lower initial dose is acceptable in clinical practice. ESC also noted that wastage was not accounted for and advised that the cost should be rounded up to the nearest whole vial – whilst recognising that likely minimal impact of this given the high number of whole vials used per patient per bleeding episode. ESC noted the NPPL updated its prices on 1 January 2023. ESC calculated that, based on acceptance of a lower initial dose, the revised equi-effective dose calculations in the pre-ESC response, and the new NPPL prices, the cost-minimised weighted price for Obizur may be $[REDACTED] per vial.

ESC noted that the economic evaluation used an indirect method for calculating the average dose per bleeding episode, through the total amounts used, the duration of treatment, the number of infusions per day, the dose per infusion and patient body weight. All steps introduced assumptions based on inconsistent pooling of parameters from primary studies. ESC noted that the commentary suggested a more direct method for estimating utilisation for the financial analyses, which was based on Australian Bleeding Disorders Registry (ABDR) data. ESC considered it inappropriate to exclude unresolved bleeds from the economic evaluation and only include outcomes based on resolved bleeds. ESC noted the pre-ESC response clarified which Obizur studies reported dosing for all subjects and which reported dosing only for subjects with resolved bleeding; however, this was not done for the comparator studies. ESC advised that calculating the cost per resolved bleed (or per bleed) for each agent, taking into account the cost of all treatment(s) used regardless of outcomes, may address some of the uncertainty in the equi-effective dose calculations, and could provide a frame of reference for a cost-effective price for Obizur (as recommended by the MSAC Executive).

ESC also noted that costs associated with hospital length of stay were excluded from the ADAR’s economic evaluation. ESC considered this may not be appropriate, as length of stay varies between individual treatments; however, data on length of stay may be difficult to interpret, as it is influenced by many clinical factors. The length of stay for patients receiving more than one of the comparator therapies has not been described, but should be included, if this data is available.

ESC also considered the market share weighting used for the comparators (78% NovoSeven and 22% FEIBA) to be uncertain, as it is based on very small patient numbers. ESC noted the pre-ESC response assumes that Obizur will substitute for NovoSeven and FEIBA in clinical practice however, ESC queried whether Obizur may be used in addition to, rather than as a substitute for, BPAs, especially for patients with a serious bleed requiring surgery.

ESC noted the pre-ESC response claimed that Obizur is likely to be cost saving to the NBA. ESC considered this highly uncertain and if there were any net savings, they would be modest, but more likely, funding Obizur would result in a low net impact. However, ESC considered the low net impact is only possible if the assumptions used to calculate the equi-effective dose are reliable. ESC noted that the average number of bleeds per patient per year estimated by the ADAR was inconsistent (lower estimate) with the estimate created using Australian utilisation data for BPAs (ABDR) in the commentary (see Section 12). Therefore, ESC considered that the financial impact estimated by the ADAR is significantly underestimated. ESC noted that, after the commentary corrected referencing and rounding errors in the ADAR and applied updated NPPL prices for BPAs (as of 1 January 2023), the estimated cost to the NBA was $[REDACTED] in year 1 increasing to $[REDACTED] in year 6.

**ESC considered that, if a risk-sharing arrangement between the NBA and supplier of Obizur is to be implemented, it should consider price reductions to address the risk of the average dose per patient per bleed being higher in practice (which would result in higher costs) than have been assumed in the ADAR.** ESC noted from the commentary (p218) that BPAs represent considerable financial cost to the Australian Government, and any proposed financial or volume cap may need to incorporate all BPAs given the uncertainty of uptake for Obizur.

## 17. Applicant comments on MSAC’s Public Summary Document

Takeda welcomes the MSAC’s recommendation for Obizur® (susoctocog alfa) to be publicly funded under the National Blood Authority’s (NBA’s) National Product Price List (NPPL) for the treatment of bleeding episodes in Australian adult patients with Acquired Haemophilia A (AHA).

## 18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](http://msac.gov.au/internet/msac/publishing.nsf/Content/Home-1)

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22. C*ell ‘C26’ of Inputs sheet of ‘CMA versus FEIBA’ workbook. Instead of dividing number of infusions by the duration of treatment, duration of treatment was divided by number of infusions* [↑](#footnote-ref-23)
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