MSAC Application 1714

National Blood Authority listing for Obizur® (susoctocog alfa) for treatment of bleeding episodes with acquired haemophilia A

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation name: Takeda Pharmaceuticals Australia Pty Ltd
ABN: 71 095 610 870
Business trading name: Takeda Pharmaceuticals Australia Pty Ltd

Primary contact name: REDACTED

Primary contact number
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☒ Yes
☐ No

(b) If yes, are you listed on the Register of Lobbyists?

☒ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

National Blood Authority (NBA) Listing for Obizur® (susoctocog alfa) for treatment of bleeding episodes in patients with acquired haemophilia A (AHA).

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

AHA, or acquired Factor VIII (FVIII) inhibitor disorder, is a condition where patients with no history of bleeding disorders present with spontaneous bleeding. Patients with AHA have normal FVIII (a protein needed for blood clotting) but develop autoantibodies (inhibitors) against their own FVIII.

AHA is rare disease, and in Australia the most recent Australian Bleeding Disorders Registry (ABDR) report shows that 12 patients received treatment in 2019/20 (NBA, 2020). AHA can be caused by an underlying autoimmune condition, malignancy or pregnancy – however, around half of all cases are idiopathic (Knoebl et al., 2012). Bleeding in AHA is distinct from the more common congenital haemophilia A, and the risk of severe complications or even death from bleeding is significant in these patients (AHCDO, 2016).

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Management of AHA involves primarily controlling acute bleeding episodes, and eradicating the inhibitors using immunosuppressive therapy (IST). Two treatment approaches for spontaneous bleeding episodes are available: 1) using bypassing agents (BPAs, concentrates of factors that bypass the acquired deficiency); or 2) strategies to increase FVIII levels. Clinical guidelines recommend that BPAs should be used in preference to FVIII plasma-derived products (AHCDO, 2016).

BPAs presently available on the Australian NBA National Product Price List ('NBA Product List') include NovoSeven® RT (recombinant activated factor VIIa [FVIIa], eptacog alfa) and activated prothrombin complex concentrate (FEIBA NF®). The major limitations of these BPAs are potential risk of thrombosis, particularly in the elderly; and lack of reliable laboratory measurements that correlate with clinical efficacy (Franchini et al., 2013). As such, treatment of bleeding is dependent on observable clinical responses, which are relatively subjective.

Susoctocog alfa (Obizur®) is a purified, recombinant (synthetic) porcine FVIII protein that is produced by genetic technologies from the FVIII gene in pigs. It is adequately different from human FVIII to either go undetected or only be partially detected by the antibody (inhibitor) to the human FVIII (also known as cross-reaction). However, the protein is still adequately similar to allow clotting to occur, subsequently stopping the bleeding. Unlike BPAs, Obizur® replaces the missing coagulation FVIII protein and enables measurement of FVIII activity using available standard FVIII assays, thereby, guiding dosing and enhancing treatment efficacy and safety.

Obizur® has clinical safety and effect with acute bleeding or during urgent surgery whilst patients are awaiting prednisolone, rituximab and/or cyclophosphamide IST to work. It provides a shorter-term stabilisation of bleeding until the anti-porcine factor VIII titres rise (generally after 5-10 days). It provides and advantage of FVIII activity and haemostasis that can be precisely measured by a one stage assay and an advantage in elderly patients where FEIBA or rFVIIa may provoke thrombosis or not achieve effective haemostasis.

6. (a) Is this a request for MBS funding?

☐ Yes
☒ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

N/A

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
☐ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
☐ A new item for a specific single consultation item
☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☒ Yes
☐ No

(g) If yes, please advise:

In 2016, the sponsor (previously Baxalta Australia) submitted a Schedule 4 application to the National Blood Authority (NBA) for Obizur® to be included on the NBA Product List. An addendum to the Schedule 4 submission was further provided in 2017. In late 2020 the NBA conducted a Cycle 1 multi-criteria analysis evaluation, which provided a description of the proposal, followed by an outline of the population, intervention, comparator and outcomes (PICO), and a high-level literature review. Following this Cycle 1 multi-criteria analysis, the NBA recommended that the Obizur application be submitted to MSAC for assessment.

The intention of this MSAC application is to request a HTA review to inform a NBA listing for a blood product, Obizur® (susoctocog alfa) for treatment of bleeding episodes with AHA. Takeda request that the MSAC submission for Obizur be reviewed under an expedited pathway given the Schedule 4 PICO review that has been completed by the NBA/JBC.

7. What is the type of service:

☒ Therapeutic medical service (blood product)
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

☐ To be used as a screening tool in asymptomatic populations
☐ Assists in establishing a diagnosis in symptomatic patients
☐ Provides information about prognosis
☐ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

N/A

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

N/A

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

N/A

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

N/A

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

N/A

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: Intravenous catheter, intravenous line

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Medicine (susoctocog alfa (bhk), Obizur®)

Manufacturer's name: **REDACTED**
Manufacture of dosage form: **REDACTED**
Sponsor's name: Takeda Pharmaceuticals Australia Pty Ltd

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☒ Yes (if yes, please provide details below)
☐ No

ARTG listing, registration or inclusion number: AUSTR 236475

TGA approved indication(s), if applicable:
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 FVIII inhibitor titre greater than 20 BU. Obizur® is not indicated for the treatment of congenital haemophilia A or von Willebrand disease.

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

N/A

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

N/A

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Retrospective case series	OBIZUR (Ellsworth et al., 2020) Recombinant porcine FVIII for bleed treatment in acquired hemophilia A: findings from a single-center, 18-patient cohort. Blood Adv. 2020 Dec 22;4(24):6240-6249.	Retrospective analysis of efficacy data for 18 AHA patients receiving Obizur® for bleeding episodes (first line and second line).	https://pubmed.ncbi.nlm.nih.gov/33351122/	2020
2.	Phase 2/3 open label trial	OBIZUR (NCT01178294) (Kruse-Jarres et al., 2015) Efficacy and safety of OBI-1, an antihaemophilic Factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia. 2015 Mar;21(2):162-170.	Phase 2/3 study designed to evaluate the efficacy of Obizur® treatment for bleeding episodes in 28 patients with AHA.	https://pubmed.ncbi.nlm.nih.gov/25623166/	2015
3.	Retrospective case series	NOVOSEVEN, FEIBA (Baudo et al., 2012) Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood. 2012 Jul 5;120(1):39-46.	Assessment of efficacy and safety of rFVIIa, aPCC, FVIII, or DDAVP for the treatment of AHA for 482 patients with bleeding in the European AHA Registry.	https://pubmed.ncbi.nlm.nih.gov/22618709/	2012
4.	Prospective case series	FEIBA (Borg et al., 2015) FEIBA in the treatment of acquired haemophilia A: results from the prospective multicentre French 'FEIBA dans l'hémophilie A acquise' (FEIBHAC) registry. Haemophilia. 2015 May;21(3):330-7.	Assessment of prospective registry efficacy and safety data for 34 AHA patients receiving FEIBA for bleeding episodes or prophylaxis at the time of invasive procedures. Patients were followed up for 3 months.	https://pubmed.ncbi.nlm.nih.gov/25359571/	2015

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
5.	Retrospective case series	FEIBA (Sallah, 2004) Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. Haemophilia. 2004 Mar;10(2):169-73.	Retrospective analysis of efficacy and safety data for 34 AHA patients receiving FEIBA for first-line bleeding episodes.	https://pubmed.ncbi.nlm.nih.gov/14962206/	2004
6.	Prospective case series	FEIBA (Zanon et al., 2015) Activated prothrombin complex concentrate (FEIBA®) for the treatment and prevention of bleeding in patients with acquired haemophilia: A sequential study. Thromb Res. 2015 Dec;136(6):1299-302.	Prospective analysis of bleeding relapse and safety for AHA patients receiving FEIBA for bleeding episodes (11 patients/bleeds).	https://pubmed.ncbi.nlm.nih.gov/26505666/	2015
7.	Retrospective/ prospective case series	FEIBA (Zanon et al., 2019) Activated prothrombin complex concentrate (FEIBA®) in acquired haemophilia A: a large multicentre Italian study - the FAIR Registry. Br J Haematol. 2019 Mar;184(5):853-855.	Retrospective analysis of efficacy and safety data for AHA patients receiving FEIBA for bleeding episodes (56 patients/bleeds).	https://pubmed.ncbi.nlm.nih.gov/29528100/	2019 (relates to Zanon 2015 publication with more patients/longer follow-up)
8.	Retrospective case series	NOVOSEVEN (Amano et al., 2017) Treatment of acute bleeding in acquired haemophilia A with recombinant activated factor VII: analysis of 10-year Japanese postmarketing surveillance data. Haemophilia. 2017 Jan;23(1):50-58. doi: 10.1111/hae.13033.	Assessment of use, efficacy and safety of rFVIIa for the treatment of AHA by analysis of 10-year post-marketing surveillance data. Data were collected for 371 bleeding episodes in 132 patients.	https://pubmed.ncbi.nlm.nih.gov/27457022/	2017
9.	Retrospective case series	NOVOSEVEN (Baudo et al., 2004) Treatment of acquired factor VIII inhibitor with recombinant activated factor VIIa: data from the Italian registry of acquired hemophilia. Haematologica. 2004 Jun;89(6):759-61.	Assessment of efficacy of rFVIIa for the treatment of AHA in 2001 in the Italian Registry of acquired haemophilia. Data were collected for 19 bleeding episodes in 10 patients.	https://pubmed.ncbi.nlm.nih.gov/15194550/	2004

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
10	Prospective case series	NOVOSEVEN (Borg et al., 2013) Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise) registry. Haemophilia. 2013 Jul;19(4):564-70.	Study of prevalence, clinical course, disease associations and outcomes for haemostatic treatment and autoantibody eradication in 82 patients with a 1-year follow-up.	https://pubmed.ncbi.nlm.nih.gov/23574453/	2013
11	Prospective case series	NOVOSEVEN (Dehmel et al., 2008) Thrombelastographic monitoring of recombinant factor VIIa in acquired haemophilia. Haemophilia. 2008 Jul;14(4):736-42.	Investigation of efficacy of rFVIIa for the treatment of acute bleeding in 10 patients with AHA.	https://pubmed.ncbi.nlm.nih.gov/18445011/	2008
12	Prospective case series	NOVOSEVEN (AQUI-7) (Guillet et al., 2021) Adaptation of recombinant activated factor VII in the treatment of acquired haemophilia A: Results from a prospective study (ACQUI-7) in France. Thrombosis Update. 2021; 2(100021):1–6.	Investigation of use, efficacy and safety of rFVIIa for the treatment of 27 bleeding episodes in 27 patients with AHA (2010 – 2013 registry data).	https://www.sciencedirect.com/science/article/pii/S2666572720300213	2021
13	Prospective case series	NOVOSEVEN (Hay, 1998) The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. Thromb Haemost. 1997 Dec;78(6):1463-7.	Investigation of efficacy and safety of rFVIIa for treatment of bleeding in 38 patients with AHA (14 first-line episodes, 60 salvage-therapy episodes).	https://pubmed.ncbi.nlm.nih.gov/9423795/	1997
14	Prospective case series	NOVOSEVEN (Lentz et al., 2014) A novel supplemental approach to capturing post-marketing safety information on recombinant factor VIIa in acquired hemophilia: the Acquired Hemophilia Surveillance project. J Blood Med. 2014 Jan 13;5:1-3.	Investigation of use, efficacy and safety of rFVIIa for treatment of bleeding in 65 patients with AH between April 2008 and 30 November 2011 from the United States AHS register.	https://pubmed.ncbi.nlm.nih.gov/24470784/	2014

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
15	Retrospective case series	NOVOSEVEN, FEIBA (Porrazzo et al., 2021) Single centre experience on Acquired Haemophilia A patients: Diagnosis, clinical management and analysis of factors predictive of response and outcome. Haemophilia. 2021 Nov;27(6):e667-e674.	Investigation of efficacy of haemostatic therapy (rFVIIa 46%, aPCC 34%) in 56 patients with AH at a single centre between 1978 – 2019.	https://pubmed.ncbi.nlm.nih.gov/34382302/	2021

AHS, Acquired Hemophilia Surveillance; aPCC, activated prothrombin complex concentrate; DDAVP, Desmopressin; FEIBA agent, Factor VIII inhibitor bypass activity agent; rFVIIa, recombinant activated factor VII

18. **Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

It is expected that the funding of Obizur® would be a matter for all Australian governments under the national blood arrangements, following recommendations from the Medical Services Advisory Committee.

The National Blood Authority (NBA) seeks advice from the Australian Haemophilia Centre Directors' Organisation (AHCDO).

20. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

N/A

21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

The relevant consumer organisation is the Haemophilia Foundation Australia.

22. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

The following four centres have had experience on a limited basis with Obizur in the treatment of AHA, as published in Campbell et al. 2020; Haemophilia Treatment Centre, Alfred Hospital, Melbourne, Victoria Australia

- Queensland Haemophilia Centre, Royal Brisbane and Women's Hospital, Brisbane, Queensland Australia
- Calvary Mater Hospital, Newcastle, New South Wales Australia
- Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria Australia

Campbell S, Mason J, Prasad R, Ambrose H, Hunt S, Tran H. Acquired haemophilia and haemostatic control with recombinant porcine factor VIII: case series. Intern Med J. 2021 Feb;51(2):215-219. doi: 10.1111/imj.14773. PMID: 32043744.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

AHA is a rare disorder caused by autoantibodies (inhibitors) to FVIII (a protein needed for blood clotting). The lack of functional FVIII in the blood, when neutralised by the auto-antibodies, results in a high risk of spontaneous bleeding, minimal trauma-associated bleeding, or undue bleeding during surgery.

In Australia the NBA ABDR Annual Report from 21 haemophilia treatment centres indicates there were 92 patients diagnosed with AHA of which 12 people received treatment in FY2019-20 (NBA, 2020). AHA can be caused by an underlying autoimmune condition or malignancy – however, around half of all cases are idiopathic (Knoebl et al., 2012). Bleeding may be life or limb-threatening, with a greater predominance of mucocutaneous, urogenital and GI bleeding sites when compared with congenital Haemophilia A (Hay, 1998). Consequently, the risk of severe complications or even death from bleeding may be significant in these patients (AHCDO, 2016). The reported mortality rate for AHA is between 3% and 20% (Stemberger et al., 2016).

In patients with AHA, even minor invasive procedures can result in significant bleeding, therefore, particular caution should be exercised during all procedures and surgery and, if possible, they should be delayed until after the FVIII inhibitor has been eradicated (Tiede et al., 2020). Acute and chronic pain are also common in patients with Haemophilia (AHCDO, 2016).

24. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

The proposed population is adult patients who are indicated for treatment of bleeding episodes with AHA (excluding patients with congenital Haemophilia A or von Willebrand disease; see Obizur® PI November 2020).

Typically, patients with AHA present with acute or recent bleeding symptoms, without a previous history of bleeding. The diagnostic tests required are the same as for NovoSeven® RT and FEIBA NF® in terms of measuring isolated prolonged activated partial thromboplastin time (APTT) and reduced FVIII coagulant activity (MBS item 65150). An additional test to monitor anti-pFVIII antibody levels prior to, or during Obizur® treatment is also required, MBS item 65159; (AHCDO, 2016, Srivastava et al., 2020). In approximately 10% cases, patients are diagnosed with AHA prior to experiencing any bleeding episodes, in which case, a prolonged APTT may be the only sign of AHA (Knoebl et al., 2012, Tiede et al., 2020).

Obizur® provides an alternative treatment for all patients with AHA in need of treatment for spontaneous bleeding episodes. Obizur® may be preferable to NovoSeven® RT and FEIBA NF® for certain patient groups such as patients with high risk of thrombotic complications or patients requiring routine clinical monitoring of FVIII activity via laboratory assays.

Similar to treatment with NovoSeven® RT and FEIBA NF® for spontaneous bleeding episodes, Obizur® should be administered in a tertiary centre or Haemophilia Treatment Centres (HTCs), in close collaboration with a physician specialised in haemophilia treatment. Bleeding in patients with haemophilia can occur at different sites, each of which require specific management (AHCDO, 2016). A haematologist or haematology specialist will assess each patient for suitability for Obizur® therapy in the clinical setting.

25. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

The following sponsors produce blood products for the treatment of patients with AHA with bleeding episodes, however these blood products are BPAs, not FVIII proteins, so they are considered the primary comparators. The sponsor names are listed here for completeness:

- Novo Nordisk Pharmaceuticals Pty Ltd (sponsor of NovoSeven® RT)
- Takeda Pharmaceuticals Australia Pty Ltd (sponsor of FEIBA NF®)

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

Clinicians consulted in 2017 have advised Obizur® is most relevant as a first-line agent in patients with severe ('major') bleeds and a low level of recombinant porcine factor VIII (rpFVIII) inhibitor activity, who require treatment to control their bleed. A draft treatment algorithm developed for Obizur® from this consultation is presented in Figure 1.

Information obtained through rpFVIII inhibitor activity testing is intended to be used as a tool to guide ongoing treatment decisions, as patients with measurable inhibitor levels can experience reduced clinical response to treatment, or may require adjustment to their Obizur® dose to achieve bleed control. Consequently, rpFVIII inhibitor testing will be performed prior to, or routinely following initiation of Obizur® (MBS item 65159). In circumstances of high rpFVIII inhibitor activity (>20 BU) and poor clinical response, an alternative treatment may be considered.

The major difference between current treatment pathway with NovoSeven® RT or FEIBA NF® and the new proposed treatment pathway with Obizur®, is that the efficacy of Obizur® can be monitored during the course of treatment, through monitoring of FVIII levels. This has clear benefits to the patient, as regular monitoring helps to mitigate the risk of serious adverse events associated with highly elevated factor activity. Active monitoring also allows the treating clinician to titrate maintenance dosing according to the needs of the patient.

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

Obizur® (susoctocog alfa) is a purified, recombinant (synthetic) porcine FVIII that is produced by genetic technologies from the FVIII gene in pigs. It is different enough from human FVIII to either go undetected or only be partially detected by the antibody to the human FVIII (also known as cross-reaction). However, the protein is still similar enough to allow clotting to occur, which stops the bleeding. Unlike BPAs, Obizur® replaces the missing coagulation FVIII protein and enables measurement of FVIII activity using available standard FVIII assays, thereby, guiding dosing and enhancing treatment efficacy and safety (Kruse-Jarres et al., 2015, Fosbury et al., 2017).

Each Obizur® vial contains nominally 500 units (U) of susoctocog alfa and is for single use only. At present in both Australia and worldwide, Obizur is only available in a 500U vial, requiring multiple vials to be reconstituted at initiation. Following reconstitution with 1 mL sterile water, Obizur® is administered via intravenous infusion at a rate of 1 – 2 mL per minute. Patients' FVIII activity should be monitored at 30 minutes after every dose (and three hours following the initial dose). Table 1 below outlines the dosing regimen for Obizur® as per the Product Information (PI).

Table 1. Dosing for treatment of bleeding episodes with Obizur®

Type of Bleeding	FVIII level required (Units per dL or % of normal)	Initial dose (Units per kg)	Subsequent dose	Frequency and duration of subsequent dosing
Minor and Moderate Superficial muscle / no neurovascular compromise, and joint	50-100	200	Titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response	Dose every 4 to 12 hours, frequency may be adjusted based on clinical response and measured FVIII levels
Major Moderate to severe intramuscular bleeding, retroperitoneal, gastrointestinal, intracranial	100-200 (To treat an acute bleed) 50-100 (After acute bleed is controlled, if required)			

dL, deciliter; kg, kilogram
Source: Obizur® Product Information Table 1 (Takeda, 2020)

International clinical experience shows that the initial dosing regimen for Obizur® in practice differs to the PI and pivotal study. Obizur® has been commercially available for several years internationally. The experience internationally is that the average dose used has continued to fall over time as clinicians become more adept at dosing in a real-world scenario and gain more experience. The MSAC submission will present this published dosing data from the real-world setting.

In line with the above real-world evidence and UK funding guidelines, Takeda is proposing in the MSAC submission that the funding criteria for the starting dose be based on clinical need and presentation by an experienced clinician in the range *100 to 200 units per kg bodyweight*.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

N/A

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Given that AHA is a rare disease, the sponsor expects that if Obizur® is included on the NBA Product List, Obizur® will be stored at tertiary centre or HTCs, along with the current treatments used for spontaneous bleeding episodes in AHA patients (NovoSeven® RT and FEIBA NF®). Therefore, a patient's access to Obizur® is considered identical to access to NovoSeven and FEIBA.

International clinical experience shows that the initial dosing regimen for Obizur® in practice differs to the PI and pivotal study. The experience internationally is that the average dose used is reduced as clinicians become more adept at dosing in a real-world scenario and gain more experience, especially with dose initiation. The MSAC submission will present this published dosing data from the real-world setting. In line with the above real-world evidence and UK funding guidelines, Takeda is proposing in the MSAC submission that the funding criteria for the starting dose be based on clinical need and presentation by an experienced clinician in the range 100 to 200 units per kg bodyweight.

At present, one vial size (500 U) is manufactured worldwide. **REDACTED**. Multiple vials are required to be reconstituted, particularly for the initiation dose.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

MBS code 65150: FVIII levels need to be tested prior to or soon after administration of Obizur® or other treatment.

MBS code 65159: anti-pFVIII inhibitor testing would be required for Obizur® use, to test for cross reacting antibody activity.

As outlined in the NBA Schedule 4 multi-criteria analysis review (April 2020), "*Expert advice to the NBA confirmed that anti-pFVIII testing would be done in tertiary centres where the expertise to perform the test reliably exists (AHCDO, 2020)"*.

32. If applicable, advise which health professionals will primarily deliver the proposed service:

Treatment with Obizur® is for inpatients at tertiary centres or HTCs under the clinical supervision of a haematologist or haematology specialist who specialises in the treatment of bleeding disorders (Obizur® PI Nov 2020). As outlined previously, Obizur® will likely be administered in HTCs, or if not possible in close collaboration with a physician specialised in haemophilia treatment.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

The administration of Obizur® cannot be delegated.

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Treatment with Obizur® is for inpatients at tertiary centres of HTCs under the clinical supervision of a haematologist or haematology specialist who specialises in the treatment of bleeding disorders (Obizur® PI Nov 2020).

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

The Royal College of Pathologists of Australasia runs a comprehensive program for haemophilia. Specialised staff involved in the diagnosis and treatment of bleeding disorders, such as AHA, participate in this program (AHCDO, 2016).

Haematologists and pathologists specialising in haemophilia have completed at least 5 years of specialist training after becoming a doctor. In Australia, most haematologists and pathologists are fellows of the Royal College of Pathologists of Australasia.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- ☐ Inpatient private hospital (admitted patient)
- ☒ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☐ Laboratory

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

FEIBA NF® and Recombinant Factor VIIa (brand name NovoSeven® RT) are BPAs listed on the NBA Product List used to treat patients that have developed inhibitors with spontaneous bleeding episodes. NovoSeven® RT is used more commonly for the treatment of severe bleeding in patients diagnosed with AHA (NBA, 2020). Similar to treatment with Obizur®, FEIBA and NovoSeven® RT should be administered in tertiary centres or HTCs for bleeding episodes, in close collaboration with a physician specialised in haemophilia treatment.

NovoSeven® RT is administered as an intravenous bolus injection whilst FEIBA NF® is administered via intravenous injection/infusion following reconstitution. See dosage regimens presented in Table 2. FEIBA NF® is contraindicated in cardiac surgery involving cardiopulmonary bypass and procedures involving extracorporeal membrane oxygenation due to the high risk of thrombotic adverse events (FEIBA NF PI 2020, NovoSeven® RT PI 2018).

Table 2. Dosage regimens for comparators NovoSeven® RT and FEIBA NF®

Product (brand, form, container)	Dosage/frequency		Duration of therapy
	Mild to moderate bleeds	Severe bleeds	
FEIBA NF® (Factor VIII inhibitor bypassing fraction) Powder for reconstitution for intravenous injection/infusion. Single-dose glass vial (500 U, 1000 U or 2000U)	50 – 75 U/kg bw every 12 hours	100 U/kg bw every 12 hours Patients should be monitored for the development of DIC, acute coronary ischemia and other thrombotic or thromboembolic events.	Treatment should be continued until clear signs of clinical improvement appear, such as pain, reduction of swelling or mobilization of the joint. A daily dose of 200 U/kg body weight should not be exceeded. Do not exceed an injection/infusion rate of 2 U/kg bw per minute.
NOVOSEVEN® RT eptacog alfa (activated) (bhk)) Powder and solvent for reconstitution for bolus injection. Single-use glass vial (1 mg, 2 mg, 5 mg or 8 mg)	90µg/kg bw every 3 hours (max 2 or 3 injections)	Up to 120µg/kg bw every 2 – 3 hours	Continue treatment until control is achieved, then treat every 3-12 hours if necessary.

bw, body weight; DIC, disseminated intravascular coagulation; kg, kilogram; mg, milligram; U, unit; µg, microgram
Source: FEIBA NF PI (Takeda, 2020b), NovoSeven® RT PI (Novo_Nordisk, 2018).

Regardless of the proposed treatment for AHA, the following MBS item is needed to test FVIII levels prior to, or soon after treatment commences:

- **MBS code 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
  Fee: $70.90 Benefit: 75% = $53.20 85% = $60.30

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes (please list all relevant MBS item numbers below)
☒ No

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

In terms of follow-up care, international guidelines recommend immunosuppressive therapy (IST) to eradicate the inhibitor, and therefore shorten the time to achieve remission. Frail patients may not be suited to IST due to higher risks of adverse events.

Patients should be closely monitored for adverse events until they achieve complete remission and for several months thereafter. Low coagulant FVIII activity should be monitored monthly during the first 6 months, every 2–3 months up to 12 months, and every 6 months during the second year and beyond, if possible. Monitoring of FVIII coagulant activity is more sensitive than APTT for detecting recurrence (Tiede et al., 2020).

Patients will receive comprehensive follow-up care via coordination. See Attachment A 'Clinical Algorithm' for schematic of management pathway of patients with AHA.

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

REDACTED

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

The clinical pathway will be essentially the same after Obizur® as it is for NovoSeven® RT/FEIBA NF® therapy. The length of hospital stay and recovery time for Obizur® treatment is expected to be similar to NovoSeven® RT/FEIBA treatment.

Although FVIII levels would be tested regardless of proposed treatment, anti-pFVIII antibody testing is an additional test required for Obizur® treatment. This test will be performed in tertiary centres (or HTCs) where the expertise to perform the test reliably exists (MBS code 65159: Quantitation of circulating coagulation factor inhibitors by Bethesda assay - 1 test, Fee: $70.90 Benefit: 75% = $53.20 85% = $60.30).

In addition, Takeda intend to provide relevant product support material and personnel to support clinicians in the management of AHA with Obizur®.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Obizur® is non-inferior to NovoSeven® RT and FEIBA in adult patients with AHA in terms of overall survival and resolved bleeding episodes.

Obizur® is non-inferior to NovoSeven® RT and FEIBA in adult patients with AHA in terms of safety.

44. Please advise if the overall clinical claim is for:

☐ Superiority
☒ Non-inferiority

45. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Serious adverse events

Thromboembolic complications related to treatment

Clinical Effectiveness Outcomes:

All-cause mortality

Resolved bleeding episodes (all bleeds, first-line treatment, second-line treatment)

Complete/partial response at 24 hours

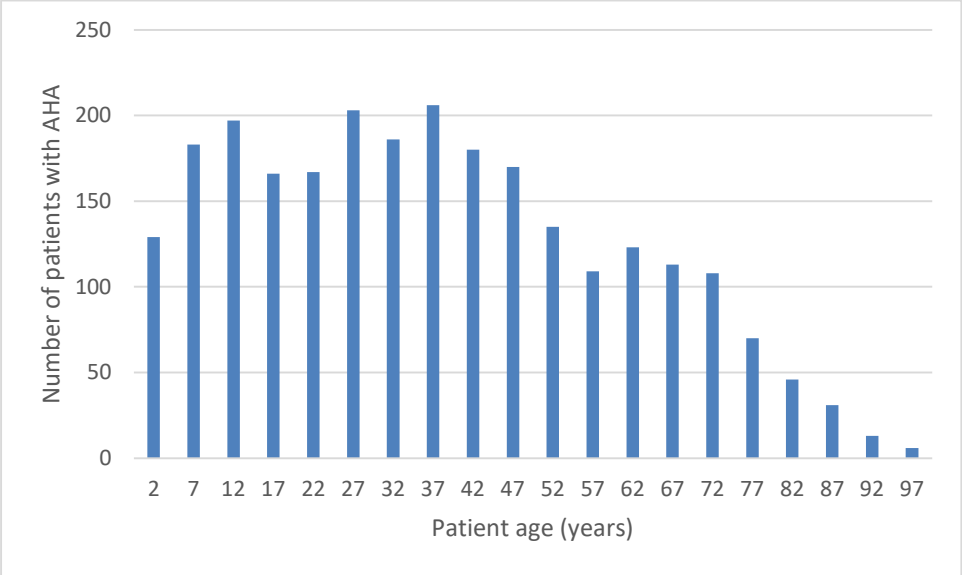
Costs (procedure, tests, ongoing monitoring)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

Haemophilia A (FVIII deficiency) is a rare disease with an annual incidence of approximately one case per one million people and predominately affects males (Figure 1). The majority of adults diagnosed with Haemophilia A have congenital Haemophilia A (97%) and the remaining 3% have AHA (AHCDO, 2016).

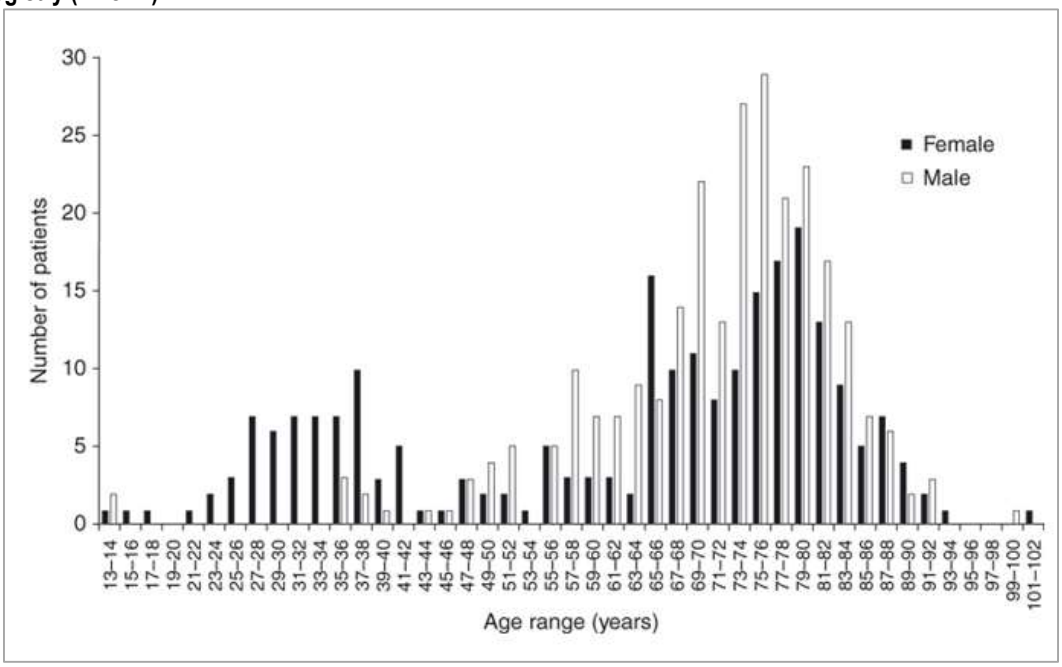
Figure 1. Histogram of age at diagnosis of Haemophilia A in Australia (FY 2019-20)



FY, financial year
Source: ABDR Annual Report Table 13 (NBA, 2020)

For patients with AHA, two peaks in incidence are typically observed; one associated with pregnancy/childbirth, and another with older age (>60 years old). The age distribution at diagnosis according to gender from the European Acquired Haemophilia Registry (EACH2) is presented in Figure 2 (median age at diagnosis: 74 years). In approximately 8% of cases in EACH2, AHA was diagnosed during pregnancy or within one year following childbirth (median age 34 years). In Australia, the number of adults diagnosed with AHA has been slightly increasing since 2017 (Figure 3) (AHCDO, 2016).

Figure 2. Histogram of age at diagnosis of AHA according to gender in the European Acquired Haemophilia Registry (EACH2)



AHA, acquired haemophilia A; EACH2, European Acquired Haemophilia Registry
Registry data of 501 patients with AHA in 13 European countries during 2003 – 2008
Source: Knoebl et al. 2012 Figure 1.

Figure 3. REDACTED

REDACTED

In terms of treatment for severe AHA, statistics from the Australian Haemophilia Centre Directors' Organisation (AHCDO) indicate that on average 16% of adult patients with AHA were treated with on-demand bypassing therapy for acute severe bleeding episodes between 2018 – 2020 (Table 3). During 2019-20, the majority of patients (9 / 12 = 75%) treated for severe AHA were males (NBA, 2020).

Table 3. AHA patients captured via the Australian Bleeding Disorders Registry (ABDR)

	Patient group	Source / calculation	Financial year				
			2015-16	2016-17	2017-18	2018-19	2019-20
A	Patients diagnosed with congenital Haemophilia A, n	NBA 2020 ABDR Table 3	2,301	2,365	2,302	2,372	2,449
B	Patients diagnosed with AHA, n	NBA 2020 ABDR Table 3	74	68	74	78	92
C	Patients (adults) diagnosed with AHA, n	ABDR 2020 Table 9	73	67	74	78	92
D	Adults with severe AHA who received on-demand bypassing therapy for acute bleeding episodes, n[a]	NBA 2020 ABDR Table 9 & Table 24	13	11	12	15	12
E	Percentage of AHA adults who received on-demand bypassing therapy for acute bleeding episodes, %	calculated (= D / C)	18%	16%	16%	19%	13%
F	Proportion of AHA adults treated with FVIII plasma-derived products	NBA 2020 ABDR Table 9 & Table 24	-	-	-	-	25%[a]
G	Proportion of AHA adults treated with NovoSeven® RT or FEIBA NF®	NBA 2020 ABDR Table 9 & Table 24	-	-	-	-	75%[a]
H	Patients with AHA treated with NovoSeven® RT or FEIBA NF®, n	NBA 2020 ABDR Table 9 & Table 24	-	-	-	-	9

ABDR, Australian Bleeding Disorders Registry; AHA, acquired haemophilia A; n, number of patients
a. Proportions estimated from number of patients receiving 'on-demand' treatment. There were 12 patients in total treated (Table 9), NovoSeven® RT n = 7 and FEIBA n = 2 (75%), FVIII products n = 3 (25%).
Dash indicates no data provided in NBA 2020 ABDR Annual Report.

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

As the proposed treatment will be followed by IST to eradicate the inhibitor, and therefore shorten the time to achieve remission, it is anticipated that treatment with Obizur® would only be delivered once per patient in their lifetime. The number of doses required for treatment depends on the severity of the bleeding episode, target FVIII levels, and on the patient´s clinical condition or development of anti-porcine FVIII antibodies around days 5-10. Following the initial dose of Obizur®, clinical response and FVIII should be measured every 4 – 12 hours to assess whether subsequent doses are required (Obizur® PI Nov 2020).

48. How many years would the proposed medical service(s) be required for the patient?

Treatment of AHA is an acute treatment, expected to be once in a lifetime.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

A market-share approach was used to derive the number of patients who will receive treatment with Obizur® based on the historical numbers of adults diagnosed with AHA and NovoSeven® RT/FEIBA NF® patient treatment numbers for acute bleeding from the ABDR. During FY 2019-20, there were seven and two patients with AHA treated for severe bleeding episodes with NovoSeven® RT or FEIBA NF® respectively (Table 4). **REDACTED**

Table 4. Actual and forecast patient numbers with AHA based on ABDR data

	Patient group	Calculation for forecast	Actual[a] ABDR data			Forecast	
			2018	2019	2020	REDACTED	REDACTED
A	Patients (adults) diagnosed with AHA, n	**REDACTED**	74	78	92	**REDACTED**	**REDACTED**
B	Percentage of adults with severe AHA who receive on-demand bypassing therapy for acute bleeding episodes, %	**REDACTED**	16%	19%	13%	**REDACTED**	**REDACTED**
C	Adults with severe AHA who receive on-demand bypassing therapy for acute bleeding episodes, n[a]		12	15	12	**REDACTED**	**REDACTED**
D	Proportion of AHA adults treated with NovoSeven® RT or FEIBA[a]	Proportion for year 2020 = 75%	NR	NR	75%	**REDACTED**	**REDACTED**
E	Adults with AHA treated with NovoSeven® RT or FEIBA, n	= C x D	NR	NR	9	**REDACTED**	**REDACTED**
	Market share assumptions						
F	NovoSeven® RT, %	Uptake of Obizur® based on clinical expert opinion, internal analysis, NBA MCA Obizur® (April 2020)	NR	NR	78%	**REDACTED**	**REDACTED**
G	FEIBA NF®, %		NR	NR	22%	**REDACTED**	**REDACTED**
H	Obizur® uptake, %		-	-	-	**REDACTED**	**REDACTED**
	Patient numbers						
I	NovoSeven® RT, n	= E x F	-	-	7	**REDACTED**	**REDACTED**
J	FEIBA NF®, n	= E x G	-	-	2	**REDACTED**	**REDACTED**
K	Obizur® uptake, n	= E x H	-	-	-	**REDACTED**	**REDACTED**
	Total, n		-	-	9	**REDACTED**	**REDACTED**

ABDR, Australian Bleeding Disorders Registry; AHA, acquired haemophilia A; FY, financial year; n, number of patients; NR, not reported in NBA 2020 ABDR Annual Report.

a. Financial years were reported in the NBA 2020 ABDR Annual Report, however this analysis assumes FY as a proxy for the following calendar year. i.e. FY 2017-18 = calendar year 2018. Refer to Table 3 for source of observed data for actual years (2018 – 2020).

b. **REDACTED**

c. Rounded up to next integer (= 2) so total equals 13, otherwise rounding error in total.

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

Treatment with Obizur® is for inpatients at tertiary centres or HTCs under the clinical supervision of a haematologist or haematology specialist. Given the very small patient numbers annually (n= 11 to 15 annually), it is unlikely that there will be capacity restraints.

REDACTED

Table 5. Determination of forecast volumes

REDACTED

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

Takeda will present a primary comparison of Obizur® versus NovoSeven® RT and FEIBA. The price of OBIZUR® will be cost-minimised to the NBA budget using the latest pricing information for NovoSeven® RT and FEIBA (NBA Product List, July 2021 prices). The price of NovoSeven® RT and FEIBA in AHA are determined by the price in congenital Haemophilia A as set out in the NBA Product List. AHA represents a very small proportion of all Haemophilia A patients in Australia (< 4% in 2019-20). Of these patients in Australia, the number who receive treatment each year for AHA ranges from n=11 to n= 15 over the past four years.

New published real-world evidence spanning four years (n= 382) is available from the UK (UKHCDO Annual Report and Bleeding Disorder Statistics). This data reports comparative dosing in AHA for Obizur®, NovoSeven® RT and FEIBA. The total patient number and total dose is reported for the three comparative products which will inform the cost-minimisation analysis. The total dose reimbursed will be divided by the total patient number to calculate the mean dose per patient and this will be compared across comparative treatments.

Patient presentation and patient treatment setting will not change as a result of the introduction of OBIZUR® and it is not expected that there will be any incremental cost impact to the NBA, hospitals or patients.

52. Specify how long the proposed medical service typically takes to perform:

The reconstitution and intravenous administration of Obizur® will typically take <10 minutes.

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

N/A

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