Australian Government

Department of Health

Application 1511:

Extended half-life clotting factor concentrates for the treatment of haemophilia A and B

PICO Confirmation

(To guide a new application to MSAC)

(Version 1.0)

Summary of PICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

The criteria outlined below were based on those proposed by the Australian Haemophilia Centre Directors Organisation (AHCDO), a pre-PASC teleconference with clinical experts and the Department of Health, and discussions by PASC.

Table 1   Population, Intervention and Comparator components for Haemophilia A and B

Component	Description	Description
Patients	Patients with Haemophilia A Subgroups: by severity (mild, moderate and severe); by age (0-6; 6-12; >12 years); by previous treatment regimen; with and without history of inhibitors	Patients with Haemophilia B Subgroups: by severity (mild, moderate and severe); by age (0-6; 6-12; >12 years); by previous treatment regimen; with and without history of inhibitors
Interventions	EHL factor VIII products i. On-demand ii. Prophylaxis iii. Surgical prophylaxis	EHL factor IX products i. On-demand ii. Prophylaxis iii. Surgical prophylaxis
Comparators	SHL factor VIII products i. On-demand ii. Prophylaxis iii. Surgical prophylaxis	SHL factor IX products i. On-demand ii. Prophylaxis iii. Surgical prophylaxis

EHL = extended half-life; SHL = standard half-life

Table 2   Outcome component for Haemophilia A and B

Outcomes	
	Safety (incidence and severity): incidence of inhibitor (neutralising antibody) formation, serious adverse events (e.g. thrombosis, allergic reactions, malignancy)
	Effectiveness: Benefits associated with increased time between infusions
	Annualised bleeding rates (ABR) — at the joint, muscle and other sites, and divided by spontaneous versus traumatic.
	Comparison of observed ABR with prior bleeding rate in individual patients when previously receiving on-demand therapy or previously receiving prophylaxis.
	Resolution of acute bleeding episodes (% resolved with one injection; % resolved with one or two injections, mean dose administered, hospitalisation rates).
	Post-surgical haemostatic response (% of procedures assessed with haemostatic response rated as either effective or good).
	Change in joint status observed (rate of development of target joints while on EHL product, rate of resolution of target joints while on EHL product, change in joint scores or other orthopaedic outcome measures from baseline status while on EHL product).
	Quality of life outcomes for patients and/or family members
	Pain
	Acceptability of treatment to patient: Compliance - percentage expected doses administered.
	Any clinical outcomes linked to compliance
	Pharmacokinetics: Incremental recovery, area under the curve (AUC), terminal half-life; clearance, time to clotting factor levels of 3 and 1 IU/dL, mean trough levels
	Correlation between pharmacokinetics and clinical outcomes.
	Cost and cost-effectiveness: Costs, cost per QALY.
	Descriptive statistics: Annualised infusion frequency and consumption

Questions for evidence review	1. How safe, effective and cost-effective are EHL factor VIII products compared to SHL factor VIII products for the treatment of Haemophilia A (on-demand, prophylaxis, or for surgical prophylaxis)? 2. How safe, effective and cost-effective are EHL factor IX products, compared to SHL factor IX products for the treatment of Haemophilia B (on-demand, prophylaxis, or for surgical prophylaxis)?

ABR = annualised bleeding rate; AUC = area under the curve; EHL = extended half life; IU = international units; QOL = Quality of Life; SHL = standard half life

In addition to the question regarding clinical superiority or at least non-inferiority of EHL clotting factor products over SHL clotting factors, the NBA will also look to MSAC for advice regarding the following questions:

1.   Taking into account the variables affecting dosing including clinical debate in relation to appropriate therapeutic trough level, and the potential range of clinician and patient responses to the potential benefits of EHL products (including clinical effectiveness, efficient maintenance of trough level, improved adherence and quality of life improvements), what are the likely clinical use scenarios of EHL products, and which of these represent use which is appropriate for public funding?

2.   Taking into account that pricing under NBA supply arrangements is established by competitive tendering where possible, and greater competition in general leads to lower tendered prices:

   a)   can the EHL clotting factor products (for each of FVIII and FIX) be considered commensurable with current products, and with each other, and if so, what is an appropriate comparison methodology for the NBA to use within tender evaluation or contract price setting processes, and

   b)   is there a maximum relative price level (compared to current products) at which public funding of EHL products is appropriate, and if so, what is the order of magnitude of this and how is it determined?

3.   For each of FVIII and FIX, is there any particular clinical need for or advantage in:
   a)   having more than one EHL product available under NBA supply arrangements, and

   b)   continuing to have current normal half-life products available under NBA supply arrangements?

4.   Is there a need for particular specialist clinicians to be involved in the prescription or management of EHL products, or for particular governance or eligibility conditions to apply to the access of EHL clotting factor products under publicly funded arrangements?

In each case, these questions should be addressed having regard to the range of current and new EHL clotting factor products for each of haemophilia A (FVIII) and haemophilia B (FIX), and the identified clinical purposes for each condition (prophylaxis, acute treatment, perioperative management, immune tolerance induction).

Population, Intervention, Comparator and Outcomes (PICO)

Population

Haemophilia A and B are X-linked genetic diseases, caused by mutations affecting the coagulation protein factors VIII (Haemophilia A) and IX (Haemophilia B). Severe disease is defined as having <1% of normal FVIII or IX clotting activity. Moderate disease is between 1 and 5% of normal clotting activity, and mild haemophilia is having between 5 and 49% of normal clotting activity (Miguelino & Powell 2014). Patients with severe haemophilia are at risk of severe, life-threatening bleeding episodes, which may occur spontaneously (Miguelino & Powell 2014). Recurrent bleeds may cause severe arthropathy, soft-tissue haematomas, and retroperitoneal and intracerebral haemorrhages (Mancuso & Mannucci 2014). When patients are untreated, they have a short life expectancy of approximately 25 years (Miguelino & Powell 2014).

Internationally, haemophilia occurs in 1 in 6000 to 10 000 males (National Blood Authority 2017a). There are currently 2,849 people with Haemophilia A and B listed on the Australian Bleeding Disorders Registry (ABDR; Table 3). Of these, 1,241 received treatment with clotting factor VIII or IX products in the 2015-16 financial year.

Table 3   Number of people in Australian Bleeding Disorders Registry (ABDR) in 2015-16

	No. in ABDR registry	Severe disease	No. who received product
Haemophilia A	2301	660	1022
Haemophilia B	548	102	219
Total	2849	762	1241

Source: (National Blood Authority 2017a).

Haemophilia is usually diagnosed by assessing the following:

- the person has a history of prolonged bleeding (e.g. with injury, surgery, dental work or other medical procedures);
- checking if there is a family history of haemophilia or bleeding problems; and
- laboratory tests on a blood sample for a person's clotting factor levels.

The majority of people in Australia with Haemophilia have their condition managed through one of 18 Haemophilia Treatment Centres (HTC), which are specialist centres that provide comprehensive care to people with haemophilia and other bleeding disorders. The comprehensive care model ensures preventative and general treatment for the complex aspects of haemophilia are given in a co-ordinated way by a multi-disciplinary team, with specialised expertise within one centre.

Intervention

The mainstay of treatment for haemophilia is the replacement of the missing or defective clotting factors. The aim is to achieve sufficient levels of that blood plasma protein level to avoid bleeding or to stop bleeding that has already occurred (Australian Haemophilia Centre Directors' Organisation 2016). Factor VIII (FVIII) products are used for haemophilia A, and clotting factor IX (FIX) products are used for haemophilia B. Products may either be plasma-derived or recombinant.

The interventions to be assessed are extended half-life (EHL) clotting factors VIII and IX. A number of EHL clotting factors have now been developed for the treatment of haemophilia A and B. These use different strategies to prolong the half-life with greater extension achieved for factor IX than factor VIII. The EHL products and methods of half-life extension are outlined in Table 4 and Table 5. The extension in half-life allows longer intervals between prophylactic doses, as the clotting factors remain elevated for longer.

Table 4 Extended half-life products for treating haemophilia A (FVIII products)

Product (trade/generic name)	Company	Method of half-life extension	TGA status	Prophylaxis regimen recommended in PI
BAX-855 (Adynovate)	Baxalta / Shire	PEGylation (20kDa)	ARTG listings: 278729, 278728, 278727, 273517	40-50 IU/kg/2 x weekly (starting dose 55 IU/kg/2 x weekly in patients <12 years of age, maximum 70 IU/kg)
BAY 81-8973 (Kovaltry)	Bayer Australia	Formulated with Heat-Shock Protein (HSP) 70	ARTG listings: 236280, 246793, 246794, 246795, 246796	Patients >12 years old: 20 – 40 IU/kg 2 or 3 times per week Patients ≤12 years old: 25 – 50 IU/kg 2 or 4 x per week or every other day
BAY 94-9027 (Damoctocog alfa pegol)	Bayer Australia	Targeted PEGylation (60kDa)	Not TGA registered.	-
CSL 627 (Afstyla)	CSL Behring	Single-chain and increased vWF binding	ARTG listings: 271638, 271637, 271636, 271635, 271634, 271633, 270335	Patients ≥12 years old: 20 – 50 IU/kg/2 or 3 x per week Patients <12 years old: 30 – 50 IU/kg/2 or 3 x per week. More frequent or higher doses may be required
N8-GP (Turoctocog Alfa Pegol)	Novo Nordisk	Glyco-PEGylation (40kDa)	Not TGA registered.	-
rFVIII-Fc (Eloctate)	Bioverativ Australia	Fc Fusion	ARTG listings: 210525, 210524, 210523, 210522, 210521, 210520, 210519	50 IU/kg every 3-5 days or 65 IU/kg/week More frequent doses up to 80 IU/kg may be required in children <12 years of age

ARTG: Australian Register of Therapeutic Goods; IU = International Units; PI = Product Information; TGA = Therapeutic Goods Administration

Table 5   Extended half-life products for treating haemophilia B (FIX products)

Product (trade/generic name)	Company	Method of half-life extension	TGA status	Prophylaxis regimen recommended in PI
N9-GP (Refixia® or Rebinyn® Nonacog beta pegol)	Novo-Nordisk	Glyco-PEGylation	Not TGA- registered FDA approved May 2017 for on-demand treatment and perioperative management of bleeding EU approval 2 June 2017	Not currently indicated for prophylaxis by FDA In EU: indicated for treatment and prophylaxis in patients 12 years and older
rFIXFc (Alprolix)	Bioverativ Australia	Fc Fusion	ARTG listings: 209227, 209226, 209225, 209224, 209223	50 IU/kg/weekly or 100 IU/kg/10 days
rIX-FP (Idelvion)	CSL Behring	Albumin Fusion	ARTG listings: 259940, 259939, 259938, 255552	Patients ≥12 years old: 25-40 IU/kg/weekly or 50-75 IU/kg/14 days

ARTG: Australian Register of Therapeutic Goods; EMA = European Medicines Agency; FDA = Food and Drug Administration (United States); IU = International Units; PI = Product Information; TGA = Therapeutic Goods Administration

In practice, clotting factor products are generally prescribed by specialist haematologists. Different types of treatment regimens may be given, depending on the patient's bleeding phenotype, disease severity, patient choice or preference, adherence, or other factors. In patients with severe haemophilia, the standard of care is primary prophylaxis with regular infusions of factor VIII or factor IX containing products. An alternative style of treatment is "on-demand", administering clotting factors only after bleeds appear.

It is assumed that patients currently receiving standard half-life (SHL) clotting factors prophylactically would continue on a prophylactic regimen if they were to swap to an EHL product. However, some patients currently on an on-demand regimen are expected to swap to a prophylactic regimen if EHL products become available (based on what occurred within trial settings internationally).

The EHL products currently listed on the Australian Register of Therapeutic Goods (ARTG) are indicated for adults and children with haemophilia A and B for:
- Control and prevention of bleeding episodes
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Perioperative management (surgical prophylaxis)

They are not indicated for the treatment of von Willebrand disease.

Very little research has been published on the use of EHL products in patients with active inhibitors or a history of inhibitors against clotting factors VIII or IX. However, some patients with active inhibitors may undergo immune tolerance induction (tolerisation) with the relevant clotting factor, and EHL products would be used in the same manner as SHL products for this purpose.

The EHL products come as a powder in single-use vials, which is reconstituted with a diluent (sterile water), and administered intravenously. EHL treatments are administered in the same manner as SHL treatments, although at a reduced frequency. Treatment is predominantly administered at home. The AHCDO guidelines for treating haemophilia state that: *"Where appropriate and possible, people with haemophilia should be managed in a home therapy setting"* (Australian Haemophilia Centre Directors' Organisation 2016). Dosing should be determined and coordinated by a

haemophilia treatment centre (Australian Haemophilia Centre Directors' Organisation 2016). Alternatively, haematologists, haemophilia nurses, or general practitioners may administer treatment. In cases of severe bleeding, patients would be treated in a Haemophilia Treatment Centre, or an emergency department.

EHL FVIII and IX products are currently available in Australia through participation in company clinical trials (National Blood Authority 2017a), but are not part of the NBA supply arrangement (National Blood Authority 2017b).

Comparator

The comparators to EHL FVIII and FIX products are SHL FVIII and FIX products. However, any data comparing one form of EHL product to another should also be included.

Prophylaxis for haemophilia A with a SHL product is usually given 2-3 times a week, or more frequently, due to the short half-life of the standard half-life FVIII products (10 – 14 hours) (Mancuso & Mannucci 2014). Standard doses for prophylaxis in Australia range from 25 to 40 IU/kg three times per week or on alternate days (Australian Haemophilia Centre Directors' Organisation 2016). Plasma-derived or recombinant FIX products have a slightly longer half-life of around 15 to 20 hours (Mancuso & Mannucci 2014). Prophylaxis for haemophilia B is therefore often approximately 40 IU/kg of FIX twice weekly. SHL products for haemophilia A and B are summarised in Table 6 and Table 7.

Recombinant clotting factors are preferred over plasma-derived products (Australian Haemophilia Centre Directors' Organisation 2016). In Australia, the most commonly used recombinant FVIII products are second generation treatments Advate (50%) Xyntha (48%), with only a small proportion of patients receiving the first generation treatment Kogenate (2%) (National Blood Authority 2017a).

Since 2003, clotting factor products have been supplied and funded under the National Blood Agreement. The National Blood Authority manages the contracts and payments for the products supplied. Those products currently funded under NBA arrangements as at 1 July 2017 have the cost of the products shown in Table 6 and Table 7. The cost of products supplied under the NBA arrangements is shared between the Commonwealth and States and Territories (63%:37%) (National Blood Authority 2017b). The amount of product used each year varies depending on the number of patients treated, the severity of their disease, the potency of inhibitors, whether prophylaxis is practiced, the number and severity of bleeds, and amount of elective surgery undertaken (National Blood Authority 2017a).

The ACPMH guidelines state that prothrombin complex concentrates (PCCs, e.g. Prothrombinex-VF) "should only be used for the treatment of haemophilia B patients where emergency replacement of FIX is required and a pure FIX concentrate is not available", pg 49 (Australian Haemophilia Centre Directors' Organisation 2016). Likewise, in an emergency, cryoprecipitate or fresh frozen plasma may be used, but only in the absence of clotting factor concentrates. These are therefore not considered comparators.

There is another treatment simultaneously being considered (Application 1510; emicizumab) which is a monoclonal antibody that is bispecific for Factor IXa and X, and mimics the action of FVIII. Emicizumab is being proposed for patients with Haemophilia A and inhibitors to FVIII. This is not being considered a comparator to EHL FVIII.

If EHL products become available under the National Blood Agreement, it is expected that EHL products would largely replace the use of SHL products for the treatment of haemophilia, although a complete switch is expected to take over a year, as most patients are only assessed by their HTC once every 6 to 12 months.

Table 6 Standard half-life products for treating haemophilia A (FVIII products)

Product (trade/generic name)	Company	ARTG listings	Prophylaxis regimen recommended in PI	Price under NBA supply arrangement (prices as at 1 July 2017)
rFVIII (Xyntha)	Pfizer	161714, 161715, 161716, 174837, 174838, 174839, 174840, 174841	10 – 50 IU/kg at least 2 x per week In some cases, particularly paediatric patients, shorter dosage intervals or higher doses may be necessary	250 IU for $90 500 IU for $180 1000 IU for $360 2000 IU for $720 3000 IU for $1080
rch FVIII rAHF-PFM (Advate)	Baxalta	100384, 100385, 100386, 100387, 136204, 150366, 214709	20 – 40 IU/kg every other day (3 or 4 x per week) In some patients, shorter dosing intervals or higher doses may be necessary	250 IU for $75 500 IU for $150 1000 IU for $300 1500 IU for $450 2000 IU for $600 3000 IU for $900
(Biostate) pdFVIII/vWF	CSL	102109, 102110, 231858, 231859, 80523	12.5 – 20 IU/kg 1 – 3 x weekly In young patients shorter dose intervals or higher doses may be necessary	250 IU for $218.14 500 IU for $436.29 1000 IU for $872.57
rFVIII (NovoEight)	Novo Nordisk	204317, 205390, 205395, 205396, 205397, 205398	Patients ≥12 years old: 20 – 50 IU/3 x per week or 20 – 40 IU/kg every other day Patients <12 years old: 25 – 60 IU/3 x per week or 25 – 50 IU every other day	-
rAHF, rFVIII (Recombinate)	Baxalta	65814, 35857, 35858	Not stated in PI	-
bhk rFVIII (Kogenate FS)	Bayer Australia Ltd	153830, 173675, 77688, 77689, 77690	10 – 50 IU/kg every 2 to 3 days In younger patients, shorter dosage intervals or higher doses may be necessary	-

ARTG: Australian Register of Therapeutic Goods; IU = International Units; NBA = National Blood Authority; PI = Product Information

Table 7   Standard half-life products for treating haemophilia B (FIX products)

Product (trade/generic name)	Company	ARTG listings	Prophylaxis regimen recommended in PI	Price under NBA supply arrangement (prices as at 1 July 2017)
rch rFIX (Rixubis)	Baxalta	204765, 204766, 204767, 204768, 204769	Patients ≥12 years old: 40 – 60 IU/kg 2 x per week Patients <12 years old: 40 – 80 IU/kg 2 x per week Shorter dosage intervals or higher doses may be necessary	250 IU for $196.50 500 IU for $393 1000 IU for $786 2000 IU for $1572 3000 IU for $2358
rch rFIX (BeneFIX)	Pfizer	128339, 128375, 128377, 128378, 203316	Appropriate dose for secondary prophylaxis has not been determined. Individualised dosing required.	250 IU for $197.5 500 IU for $395 1000 IU for $790 2000 IU for $1580 3000 IU for $2370
pdFIX (MonoFIX-VF)	CSL	101710, 101711, 127476, 128007, 64759, 66066, 66208, 66301, 81649	25 – 40 IU/kg 2 x per week	$872.57 per 1000 IU

ARTG: Australian Register of Therapeutic Goods; IU = International Units; NBA = National Blood Authority; PI = Product Information

Outcomes

Patient-relevant outcomes

EHL FVIII and FIX products are at least as effective as SHL FVIII and FIX products for preventing break-through bleeds (for those receiving prophylaxis) or for quickly resolving bleeds for patients on an on-demand treatment regimen (Newton et al. 2017). A reduction in bleeding episodes may also result in superior joint status, and reduced pain. The combination of fewer administrations, reduced bleeding and improved joint status and pain should also result in quality of life benefits. There is some evidence that longer intervals between prophylactic doses are associated with better compliance for on-schedule infusions (Newton et al. 2017).

The harms associated with EHL products appear to be the same as for SHL products. There is a risk that patients will have an allergic reaction, thrombotic events, develop inhibitors, or a malignancy.

Although the key outcomes of interest are those which are directly patient-relevant, PASC noted that it will be necessary to define extension of the half-life for each EHL product. The link between pharmacokinetic outcomes and clinical outcomes should be determined, where possible.

Healthcare system outcomes

With a switch to EHL products, dosing of FVIII and FIX products are required less often. For those patients who have their treatment administered by haematologists, haemophilia nurses or general practitioners (rather than self-administering), the EHL products will reduce the costs associated with these professionals. If fewer break-through bleeds occur outside of haemophilia treatment centre

business hours, emergency department costs will be reduced. Expert opinion suggests that fewer port-a-caths would be inserted with the use of EHL products, which would reduce infection risks.[1]

In the longer-term, a reduction in the number of bleeds will result in superior joint status. There will therefore be a reduction in costs associated with managing damaged joints, such as rheumatology, physiotherapy, synovectomy, joint replacement, and non-steroidal anti-inflammatory drugs.

Current clinical management algorithm for identified population

Clinical management algorithms help to demonstrate what current practice is, and how this will be altered if the proposed intervention is incorporated into current practice. Figure 1 shows the current clinical management algorithm for patients receiving routine prophylaxis or on-demand treatment, as well as surgical prophylaxis for bleeding control in the perioperative setting. In the current clinical setting, SHL products are used in all of these settings. **Error! Reference source not found.** shows the proposed clinical management algorithms, with EHL products as a replacement for SHL products for those undergoing prophylaxis, and as alternative to SHL products for those receiving on-demand treatment.
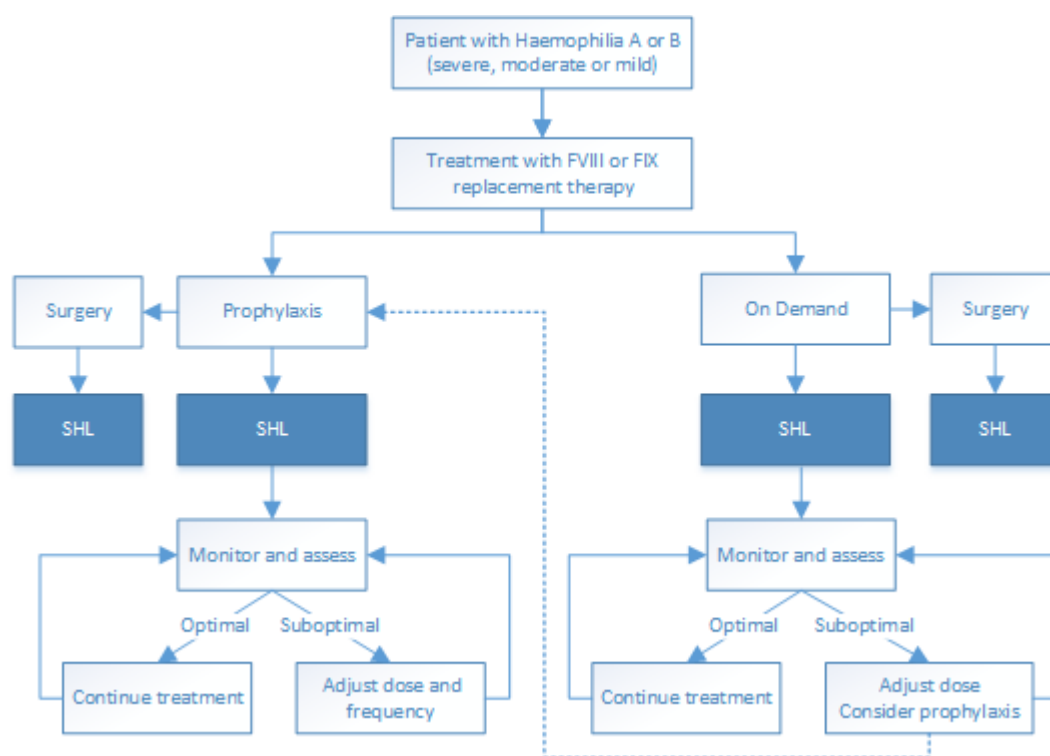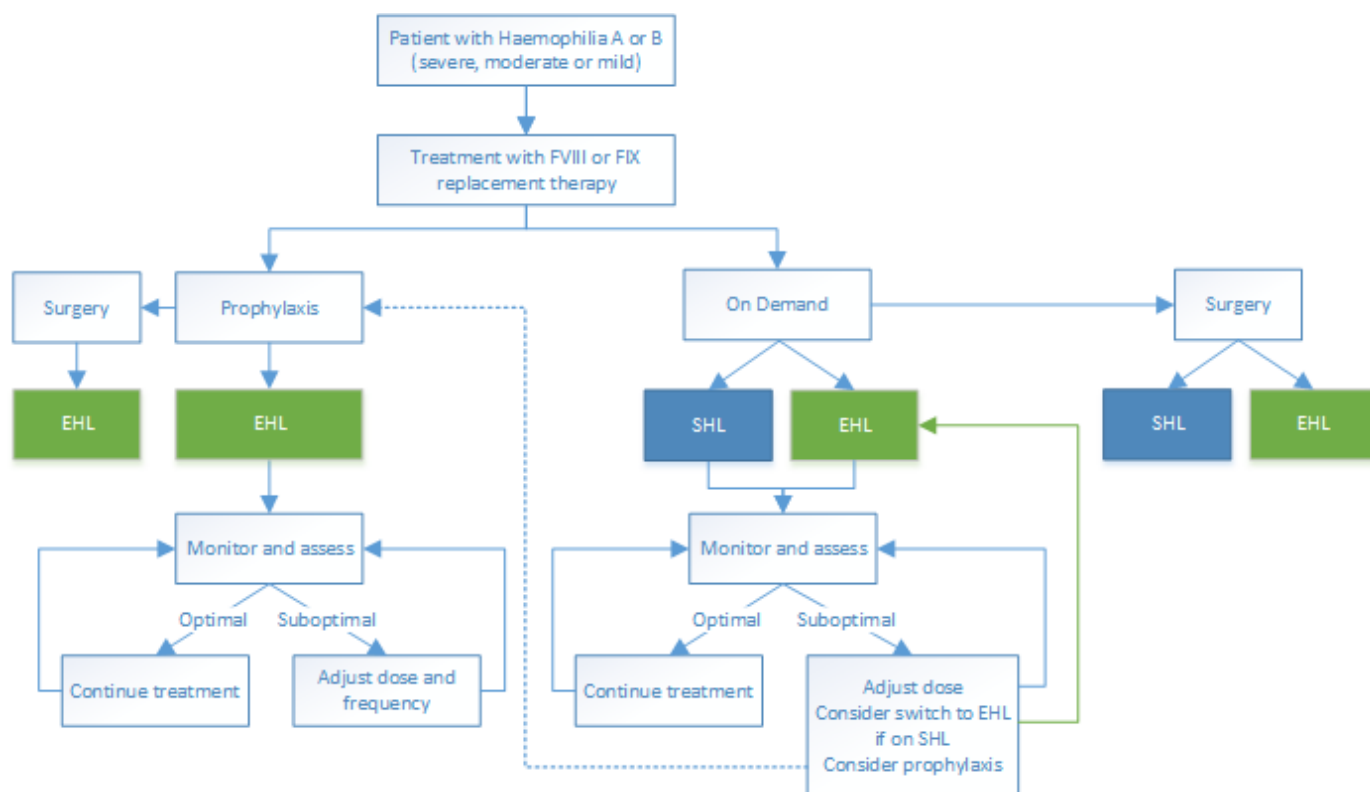

Figure 1 Current clinical management algorithm for haemophilia A and B
Source: adapted from algorithms received from CSL Behring, permission received to reproduce

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[1] Dr J. Curtin, Haematologist, via pre-PASC teleconference, 17th October 2017

Source: adapted from algorithms received from CSL Behring, permission received to reproduce

Figure 2 Proposed clinical management algorithm for haemophilia A and B

Proposed clinical management algorithm for identified population

The main change in the clinical management algorithms outlined are the replacement of SHL products with EHL products for those receiving prophylaxis, and the additional option of EHL products for those receiving on-demand treatment. For those on prophylaxis, this would involve an increase in the interval between doses. With EHL products available, it is expected that an increased number of patients would choose to switch from an on-demand regimen to a prophylaxis regimen.

Proposed economic evaluation

A systematic literature review of published evidence (searches performed November 2016) and additional information submitted by companies producing EHL products (received December 2016 to February 2017) was performed for the Australian Haemophilia Centre Directors' Organisation (AHCDO) (Newton et al. 2017). The review found that EHL products used prophylactically were superior to SHL products at preventing bleeding episodes, and improving quality of life. EHL products are as safe as SHL products. The proposed economic evaluation is therefore a cost-effectiveness or cost-utility analysis.

For on-demand regimens, it is expected that the economic evaluation will be a cost-minimisation analysis, based on non-inferior effectiveness and non-inferior safety.

Costs will be based on annualised costs (and measures of outcome) rather than cost per IU. PASC suggested that consumable and out-of-pocket costs should be assessed for SHL and EHL products.

The PASC Policy Paper stated that issues relating to cost to be considered are:

- current (including overseas) and proposed product price (i.e. product acquisition costs (if known), including whether justification or inputs have been provided for the price, and the relationship to the price of current short half-life products;
- given the NBA conducts national tendering for imported blood products, the price level (if any) where a tendered price may not be justifiable;
- consumable costs (for the service provider) and out-of-pocket expenses for patients, if any;
- ambulance, emergency department and hospitalisation costs, noting that these may already be occurring;
- additional training costs for patients and caregivers, noting these may already be occurring;
- cost offsets (e.g. fewer drug administrations, decreased use of by-pass agents and infusions, decreased orthopaedic procedures because of reduced bleeds into joints, decreased bleed management costs, decreased pain, longer intervals between prophylactic doses (with associated improved compliance with scheduled infusions), comparator differences between lost/improved patient productivity, unpaid labour by caregivers, and haemophilia-related disability; and
- validity of comparison of costs, based on annualised rates, rather than per unit costs, as proposed by potential suppliers.

Proposed item descriptor

Not applicable. Public funding of EHL products is sought. This is managed by the National Blood Authority (NBA). The NBA provides supply through centralised national contracting, where the product price is established through competitive tendering between alternative brands of functionally comparable products (registered in Australia) where possible. In the case of EHL products, there are a number of potential suppliers with similar EHL products, and a coordinated health technology assessment is planned in order to guide governments' policy decision making and NBA tendering and implementation of supply arrangements. Funding is implemented by the blood-related product being listed on the National Product List (NPL).

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