



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1511 – Extended half-life clotting factor concentrates for the treatment of haemophilia A and B

Applicant: National Blood Authority

Date of MSAC consideration: MSAC 73rd Meeting, 26-27 July 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

The application is to inform public funding for extended half-life (EHL) clotting factors VIII and IX products through the national blood arrangements.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC supported the inclusion of extended half-life clotting factor concentrates (factors VIII and IX) in the National Products Price List maintained by the National Blood Authority (NBA). MSAC gave detailed advice on establishing prices for the requested products, relative to the existing standard half-life products, and advised that appropriate risk-sharing arrangements be implemented to manage the budget uncertainties associated with these listings.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application is seeking health technology assessment advice on the evidence for EHL clotting factors VIII and IX compared to currently available options, in order to inform future public funding through the NBA.

MSAC noted that the incidence of haemophilia A (caused by deficiency of factor VIII) is approximately 1 in 10,000, and the incidence of haemophilia B (caused by deficiency of factor IX) is approximately 1 in 50,000. Female carriers of gene mutations for coagulation protein factors may also exhibit symptoms. MSAC noted that there is a high disease burden in patients with moderate and severe haemophilia. Recurrent bleeding can cause arthropathy, intracranial and retroperitoneal bleeds, and haematomas. If untreated, haemophilia reduces life expectancy to 25 years; if treated, normal life expectancy can be maintained or reduced by less than 10 years.

MSAC noted that patients managed with prophylactic products require infrequent hospital admission for bleeding episodes, and each bleed requires 2–4 days absence from work. Recurrent bleeding episodes may lead to the need for joint replacements. This occurs mainly

in the older population (55 years and older), but is less likely with prophylactic treatment, and has become less common.

MSAC noted that approximately 80% of clotting factor use is for prophylaxis to prevent or reduce the frequency of bleeding episodes (i.e. standard care for patients with haemophilia). The remainder is on-demand use to control or prevent bleeding episodes. Treatment is provided by a haematologist, and most patients are treated at haemophilia treatment centres. MSAC noted that prophylactic dosing consists of standardised regimes to achieve target trough levels and low annual bleed rates (ABR), or individualised treatment regimes in difficult-to-manage patients. Clotting factors are administered using Portacaths in children under 13 years of age. Clotting factors are also used as surgical prophylaxis, in order to better control bleeding in the context of planned surgery.

MSAC noted that there is high heterogeneity in treatment regimens according to the individual EHL product, age of the patient and individualisation of treatment.

MSAC noted that EHL clotting factors are produced by combining the recombinant factor VIII or IX with Fc (antibody fragments) or polyethylene glycol (PEG). MSAC noted that EHL factor IX products for haemophilia B have a half-life approximately 4 times longer than standard half-life (SHL) factor IX products, which has a significant impact for patients by reducing dosing frequency. The difference in half-lives is not so significant across EHL and SHL factor VIII products for haemophilia A. MSAC acknowledged that even one less dose per week would be valuable to patients.

Overall, MSAC noted that the level of evidence presented for safety and effectiveness of EHL products compared with SHL products was low across all EHL products and across different age ranges. The evidence base consisted largely of comparative studies with historical controls, or case series with before-and-after data. Treatment regimens in different studies were not similar.

MSAC noted from this evidence that EHL factor VIII products appeared to slightly reduce ABRs compared with SHL factor VIII products, but there was no significant difference in terms of quality of life. MSAC also noted some evidence that adherence to treatment was higher for EHL factor VIII than for SHL factor VIII products, but there were no direct comparisons of these EHL and SHL products.

MSAC noted from this evidence that EHL factor IX products appeared to reduce ABRs and improve quality of life compared with SHL factor IX products. Some evidence showed higher adherence with EHL factor IX products than for SHL factor IX products.

MSAC considered there was little basis to be confident that the estimated reductions in ABRs would translate into longer-term differences in patient-relevant outcomes. Although this potential could not be excluded, even the optimistic modelling of this translation of EHL products to address the residual unmet clinical need with the existing SHL products suggested that any incremental benefit would be small.

MSAC noted that the safety of EHL products is similar to that of SHL products. The rate of serious adverse events after receiving EHL products appears to be low (<1%). MSAC noted that EHL products appear to be no more likely than SHL products to result in development of inhibitors.

MSAC noted that EHL products of both factor VIII and factor IX extend the duration of action, compared with SHL products. MSAC noted that this might reduce consumption;

however, this is hard to quantify due to the poor quality data available to assess this outcome. The A-LONG trial suggested reduced consumption with the use of EHL factor VIII products, but the study was not specifically designed to measure this. MSAC noted a number of studies in adults and children which showed significantly reduced consumption with the use of EHL factor IX products.

MSAC noted that, in clinical practice, EHL products may directly replace SHL products in either individualised dosing or standardised dosing prophylaxis regimens to reduce dose frequency, , . However, MSAC noted that, for on-demand use and surgical prophylaxis, there is insufficient evidence to support a clinical claim for EHL relative to SHL products. SHL products should continue to be used for these purposes.

For prophylactic use, MSAC concluded from the evidence available that there was little clinically-important improvement in patient outcomes between the two types of products, but accepted that EHL products would reduce dosing frequency.

MSAC commented that interpretation of the economic analysis was difficult. The ICERs were highly variable depending on the age group and source data used to inform the annualised number of factor doses and bleeding rates. ICERs were highly sensitive to changes in relative factor consumption, and it is uncertain whether study estimates will be realised in practice. Although MSAC considered that the base case ICERs might underestimate the benefit of EHL products (due to simplistic modelling and factor reduction data used), the committee noted that sensitivity analyses seeking to translate ABRs into later patient-relevant outcomes did not substantially improve the ICERs.

MSAC noted that the economic model was sensitive to differences in prices between EHL and SHL products. Because there is uncertainty about what the supplier price will be, sensitivity analyses also explored the effect of different prices on the ICER.

MSAC noted that the financial implications of funding EHL products are dependent on the rate of uptake, changes in factor consumption and the price per unit.

MSAC noted that the most appropriate funding scenario is where the use of EHL products reduces dosing frequency in non-surgical prophylaxis. MSAC acknowledged that patients with poorly controlled haemophilia may benefit from individualised trough targeting.

MSAC therefore recommended a cost-minimisation approach be adopted to generate suitable price relativity between EHL and SHL products for factor VIII and IX for prophylactic use. This approach would result in the same cost per patient to achieve the same effect per patient (at least), based on observed comparative consumption data as a weighted average across the studies presented:

- factor VIII – a price increase in relative terms of about **redacted** per IU for EHL products over SHL products
- factor IX – a price increase in relative terms of about **redacted** per IU for EHL products over SHL products.

The reasons for adopting this approach to determine EHL pricing for use in prophylaxis (rather than any other approach) are that:

- it is most directly based on the study level evidence of use from which MSAC determined that EHL products are non-inferior to SHL products
- estimating the increase in relative terms is less subject to variability across baseline doses than estimating the increase in absolute terms.

MSAC considered that the evidence did not support any clinical advantage or usage differential between EHL and SHL products for on-demand or surgical prophylaxis use, and therefore recommended there either be no price differential per IU between these products for these uses, or the funding of EHL products via the NBA should exclude these uses.

MSAC recommended that there is a need for more than one EHL product in the market to meet the NBA's desire for security of supply. MSAC therefore also advised that the evidence did not support any clinical or usage differential between each of the EHL products for either factor VIII or factor IX. As such, MSAC recommended that there be no price differential across the EHL factor VIII products or across the EHL factor IX products, which is consistent with the accepted current lack of clinical basis to justify a price differential across the SHL factor VIII products or across the SHL factor IX products.

MSAC further advised that, if the on-demand or surgical prophylaxis use of EHL products cannot be excluded, then a single price should be derived for EHL factor VIII products and a single price should be derived for EHL factor IX products. Each price should be weighted by proportions of use of these products for these different purposes. Noting the proportions of patients may be difficult to estimate (and there may be changes in these proportions over time), MSAC advised that the NBA introduce appropriate risk-sharing arrangements with product suppliers of factors VIII and IX, to manage budget uncertainties associated with these listings.

4. Background

MSAC has not considered this application before.

5. Prerequisites to implementation of any funding advice

Recombinant blood products, including these EHL clotting factors, are regulated in Australia by the Therapeutic Goods Administration (TGA) as biological medicines.

6. Proposal for public funding

The proposal for public funding was for EHL factor VIII and IX products through the national blood arrangements

7. Summary of Public Consultation Feedback/Consumer Issues

Six public consultation responses were received (3 companies, 1 haematologist, and 2 professional organisations). The responses received stated that EHL products can raise a persons' factor VIII or factor IX trough level, reduce infusion frequency and the frequency of bleeds. This can have a large benefit to the patient and to their parents/carers.

8. Proposed intervention's place in clinical management

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. EHL recombinant clotting factor products are used for the treatment of haemophilia A and B.

The current clinical management algorithm for patients receiving routine prophylaxis or on-demand treatment is shown in Figure 1. **Figure 2** shows the proposed clinical management algorithm, 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.

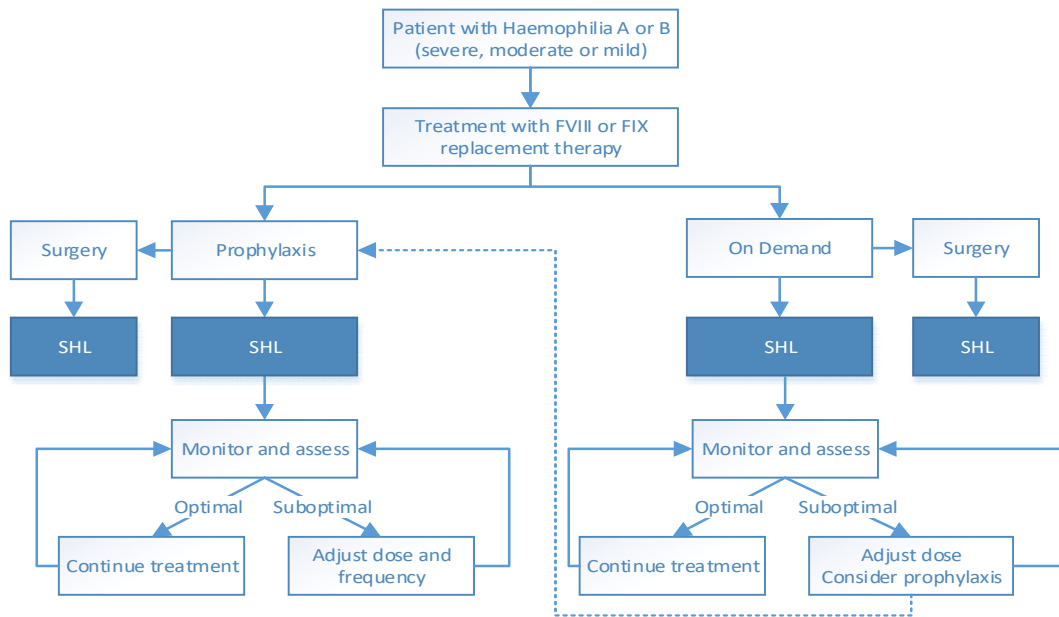


Figure 1 Current clinical pathway for delivery of SHL factor VIII and factor IX products for prophylactic and on demand treatment of haemophilia A and B

FVIII = factor VIII; FIX = factor IX; SHL = standard half-life products

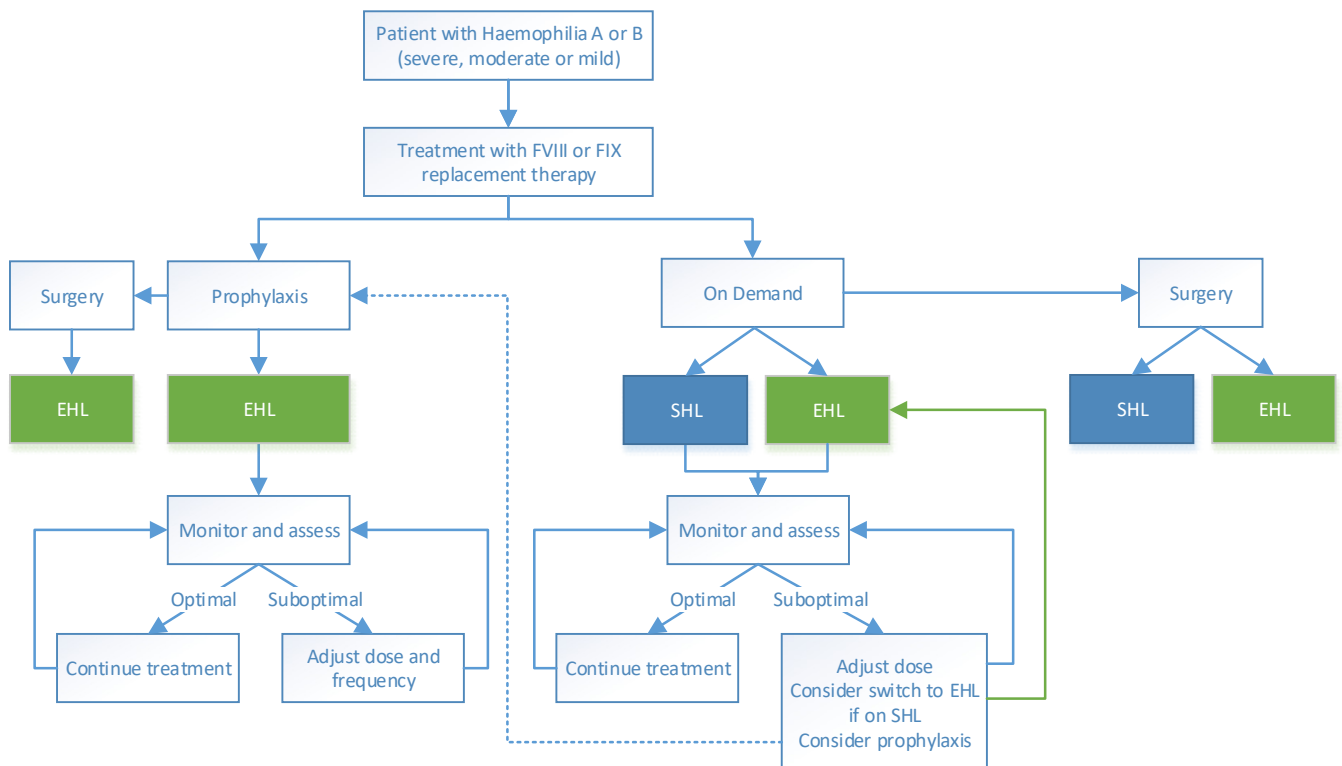


Figure 2 Proposed clinical pathway for delivery of EHL factor VIII and factor IX products for prophylactic and on demand treatment of haemophilia A and B

EHL = extended half-life products FVIII = factor VIII; FIX = factor IX; SHL = standard half-life products

9. Comparator

The main comparator comprises SHL factor VIII or factor IX containing products. For patients with severe haemophilia, the main form of treatment is prophylaxis with regular infusions of SHL factor products. Alternative styles of treatment include “on-demand”, administering SHL factor products only after bleeds appear, and “surgical prophylaxis” administering SHL factor products before planned surgery.

10. Comparative safety

Haemophilia A

No studies directly compared the safety of SHL products and EHL products. However, the overall rate of adverse events due to EHL products was low, and there were no data to suggest that EHL products are associated with a higher rate of adverse events than SHL products. Non-comparative studies reported a total of five serious adverse events related to the EHL product occurred in adults and nine in children - the majority being hypersensitivity.

Haemophilia B

There were no data to suggest that EHL products are associated with a higher rate of adverse events than SHL products.

11. Comparative effectiveness

Haemophilia A

The primary clinical outcome of interest was annualised bleeding rate (ABR). Four EHL products (BAX 855, BAY 81-8973, N8-GP and rFVIII^{Fc}) provided historical data on bleeding rates of patients when they were receiving SHL factors. In these studies, the ABRs in the patients receiving prophylactic treatment with EHL products were between 11-83% of the rates of patients receiving SHL prophylaxis.

Haemophilia B

The primary clinical outcome of interest was ABR. All studies comparing prophylaxis with SHL factor IX products (historical data) with prophylaxis with EHL factor IX products (trial data) in adolescents and adults reported that bleeding rates were reduced through the use of EHL products. Likewise, bleeding rates in those treated on-demand with EHL products were reduced compared to historical bleeding rates in those treated on-demand with SHL products.

12. Economic evaluation

Based on the clinical claims presented, cost-utility analyses were conducted for patients switching from SHL prophylaxis to EHL prophylaxis. Cost-effectiveness analyses were presented estimating a cost per infusion avoided and cost per bleed avoided.

Haemophilia A

A summary of the results of the economic analyses are presented in Table 1.

Table 1 Summary of the results of the economic evaluations, haemophilia A

	ICERs				
	One year analyses				Lifetime
	<6	6-11	12-17	18+	
Base case analysis					
Incremental cost	\$2,476	\$1,427	\$15,842	\$24,737	\$287,093
Incremental QALYs	0.0368	0.0307	0.0510	0.0510	0.8790
ICER per QALY gained	\$67,266	\$46,526	\$310,537	\$484,887	\$326,589
No. bleeds avoided	1.5	0.49	3.9	3.9	54.8
ICER per bleed avoided	\$1,651	\$2,912	\$4,062	\$6,343	\$5,235
No. infusions avoided	80	79	83	83	1,622
ICER per infusion avoided	\$31	\$18	\$191	\$298	\$177

The analyses were most sensitive to the source of data used to inform comparative factor VIII consumption and ABR, and the frequency of SHL factor VIII infusion. The analyses were also moderately sensitive to reductions in EHL factor VIII use to treat a bleed.

Haemophilia B

A summary of the results of the economic analyses are presented in Table 2.

Table 2 Summary of the results of the economic evaluations, haemophilia B

	ICERs				
	One year analyses				Lifetime
	<6	6-11	12-17	18+	
Base case analysis					
Incremental cost	\$4,003	\$29,911	-\$6,845	-\$10,688	\$28,292
Incremental QALYs	0.0820	0.0820	0.0820	0.0820	1.6298
ICER per QALY gained	\$48,811	\$364,769	Dominant	Dominant	\$17,359
No. bleeds avoided	1.90	-0.10	2.60	2.60	37.6
ICER per bleed avoided	\$2,107	Dominated	Dominant	Dominant	\$753
No. infusions avoided	54	52	55	55	1079
ICER per infusion avoided	\$74	\$576	Dominant	Dominant	\$26

The analyses were most sensitive to the source of data used to inform comparative factor IX consumption and ABR and to utility weights used.

13. Financial/budgetary impacts

A market-based approach is used to estimate the financial implications for the introduction of EHL factors for haemophilia treatment. These were based on data reported in the ABDR Annual Report 2015-16 (NBA 2017).

The financial implications resulting from the funding of EHL factor concentrates are summarised in Table 1 and Table 2, for haemophilia A and B, respectively.

Haemophilia A

Table 1 Estimation of the financial impact of funding EHL factor VIII products

	2018–19	2019–20	2020–21	2021–22	2022–23	2023–24
Projected number of people with HA	2,555	2,626	2,697	2,769	2,840	2,912
Number who received product (45.1%)	1,151	1,183	1,215	1,247	1,280	1,312
Prophylaxis						
Number on factor prophylaxis (53.8%)	619	636	653	671	688	705
Proportion who switch	60%	70%	80%	85%	90%	95%
Number of people who switch	371	445	523	570	619	670
No. of EHL IUs (226,775IU/person/year) ^a	84,205,267	100,985,230	118,549,694	129,293,178	140,428,912	151,956,896
EHL cost (\$redacted per IU)	redacted	redacted	redacted	redacted	redacted	redacted
No. of SHL IUs (229,066IU/person/year)	85,055,825	102,005,283	119,747,166	130,599,170	141,847,386	153,491,814
SHL cost (\$0.36 per IU)	\$30,974,089	\$37,146,436	\$43,607,353	\$47,559,239	\$51,655,411	\$55,895,868
Net prophylaxis cost	redacted	redacted	redacted	redacted	redacted	redacted
On demand						
Number on demand (46.2%)	532	547	562	577	592	606
Proportion who switch	60%	70%	80%	85%	90%	95%
Number of people who switch	319	383	449	490	532	576
No. of EHL IUs (65,385IU/person/year) ^b	20,875,823	25,035,843	29,390,353	32,053,833	34,814,558	37,672,529
EHL cost (\$redacted per IU)	redacted	redacted	redacted	redacted	redacted	redacted
No. of SHL IUs (65,385IU/person/year)	20,875,823	25,035,843	29,390,353	32,053,833	34,814,558	37,672,529
SHL cost (\$0.36 per IU)	\$7,602,179	\$9,117,100	\$10,702,846	\$11,672,784	\$12,678,135	\$13,718,899
Net on demand cost	redacted	redacted	redacted	redacted	redacted	redacted
Net cost of EHL factor VIII	redacted	redacted	redacted	redacted	redacted	redacted

EHL = extended half-life; HA=haemophilia A; IU = international unit; SHL = standard half-life.

^a The average number of SHL factor VIII IUs per person per year was estimated from the ABDR Annual Report 2015-16 (NBA 2017). The percentage decrease in factor VIII use, as estimated in the economic analysis, was then applied to this estimate.

^b No difference in factor VIII consumption has been assumed for on demand use. This was tested in sensitivity analyses.

Haemophilia B

Table 2 Estimation of the financial impact of funding EHL factor IX products

	2018–19	2019–20	2020–21	2021–22	2022–23	2023–24
Projected number of people with HB	579	590	601	611	622	633
Number who received product (39.6%)	230	234	238	242	247	251
Prophylaxis						
Number on factor prophylaxis (37.6%)	86	88	90	91	93	94
Proportion who switch	60%	70%	80%	85%	90%	95%
Number of people who switch	52	62	72	77	83	90
No. of EHL IUs (100,732IU/person/year) ^a	5,218,623	6,200,889	7,215,296	7,802,853	8,406,480	9,026,179
EHL cost (\$redacted per IU)	redacted	redacted	redacted	redacted	redacted	redacted
No. of SHL IUs (201,463IU/person/year)	10,437,246	12,401,777	14,430,591	15,605,705	16,812,960	18,052,357
SHL cost (\$0.79 per IU)	\$8,266,280	\$9,822,185	\$11,429,002	\$12,359,690	\$13,315,834	\$14,297,434
Net prophylaxis cost	redacted	redacted	redacted	redacted	redacted	redacted
On demand						
Number on demand (62.4%)	143	146	148	151	154	156
Proportion who switch	60%	70%	80%	85%	90%	95%
Number of people who switch	86	102	119	128	138	149
No. of EHL IUs (65,996IU/person/year) ^b	5,670,672	6,738,024	7,840,301	8,478,753	9,134,669	9,808,047
EHL cost (\$redacted per IU)	redacted	redacted	redacted	redacted	redacted	redacted
No. of SHL IUs (65,996IU/person/year)	5,670,672	6,738,024	7,840,301	8,478,753	9,134,669	9,808,047
SHL cost (\$0.79 per IU)	\$4,491,162	\$5,336,502	\$6,209,504	\$6,715,157	\$7,234,641	\$7,767,955
Net on demand cost	redacted	redacted	redacted	redacted	redacted	redacted
Net cost of EHL factor IX	redacted	redacted	redacted	redacted	redacted	redacted

EHL = extended half-life; B=haemophilia B; IU = international unit; SHL = standard half-life.

^a The average number of SHL factor IX IUs per person per year was estimated from the ABDR Annual Report 2015-16 (NBA 2017). The percentage decrease in factor IX use, as estimated in the economic analysis, was then applied to this estimate.

^b No difference in factor IX consumption has been assumed for on demand use. This was tested in sensitivity analyses.

14. Key issues from ESC for MSAC

ESC KEY ISSUES	ESC ADVICE
Clinical evidence base is poor with little direct comparative evidence	No clinical reason to doubt the comparative safety and effectiveness findings from low-level studies
The PK-data suggest considerable half-life variation between EHL products	This may have implications for negotiating unit cost of different products
Section F– Q4	<p>No change from current process for standard half-life (SHL) products.</p> <p>No specific limitation on the type of clinician who can prescribe or authorise factor VIII and factor IX products, but in practice it tends to be haematologists because of the concentration of clinical care at specialised haemophilia care centres.</p> <p>The majority of people with these conditions are treated at Haemophilia Treatment Centres (HTCs).</p>
Economic issues	<ul style="list-style-type: none"> • The interpretation of the analyses are difficult; the ICERs are highly variable depending on age group and the source data used to inform annualised doses of factor and/or bleeding rates • The ICERs are highly sensitive to changes in relative factor consumption. Uncertain if trial results will be realized in practice • ICERs likely underestimate benefit due to simplistic modelling structure and factor reduction used • Price sensitive – uncertainty as to supplier price. Analyses have been presented exploring the effect of different prices on the ICERs. • Financial implications dependent on rate of uptake, change in factor use and price per IU

ESC discussion

ESC noted that this was not an application for listing on the MBS. As such, there is no proposed MBS item descriptor.

ESC noted that haemophilia A and B are X-linked genetic diseases, caused by mutations affecting the coagulation protein factors VIII (causing haemophilia A) and factor IX (causing haemophilia B). Treatment with clotting factor VIII and clotting factor IX is required for people affected by haemophilia A or B, respectively. ESC noted that there are two main approaches to treatment: preventive (to prevent episodes of bleeding and subsequent joint and muscle damage), and on-demand (to treat clinically significant bleeding episodes).

ESC noted that the extension in half-life allows longer intervals between prophylactic doses, and/or a higher trough level to be maintained, as the clotting factors remain elevated for longer compared with short half-life products.

ESC noted that regarding comparative safety, for prophylaxis:

- EHL factor VIII has non-inferior safety for adults, adolescents and children with haemophilia A, compared with SHL factor VIII products; and
- EHL factor IX has non-inferior safety in adults, adolescents and children with haemophilia B, compared with SHL factor IX products.

ESC noted that regarding comparative safety for other uses, there is insufficient evidence to support a clinical claim for either EHL factor VIII or factor IX relative to SHL products.

ESC noted that the clinical data consisted of low-level evidence, and that no data from randomised controlled trials or head-to-head trials were provided. ESC noted that the submission included two systematic reviews, one of which was an indirect comparison of SHL and EHL products, and one matched adjusted indirect comparison of SHL and EHL products. Based on this evidence, ESC noted that, compared to SHL products:

- EHL factor VIII has superior effectiveness to SHL factor VIII for prophylaxis of haemophilia A in adults, adolescents and children
- EHL factor IX has superior effectiveness to SHL factor IX for prophylaxis of haemophilia B in adults and adolescents
- evidence is insufficient to support a clinical claim of superiority of EHL factor IX over SHL factor IX for prophylaxis in children with haemophilia B; and
- evidence is insufficient to support a clinical claim of superiority of either EHL product for on-demand and surgical prophylaxis compared to SHL products for either haemophilia A or B.

ESC considered that, although the data were from studies with low-level evidence, the findings were clinically plausible. ESC noted that all trials were conducted in moderately-severe to severe haemophilia A or B, previously treated patients, with no history of inhibitors. ESC considered that, although the safety and effectiveness of EHL products outside this population are therefore unknown, there was no reason to believe that the evidence for moderate and severe disease should not also apply to mild disease.

ESC noted that adherence rates were higher for EHL products compared with SHL products (85% versus 65%, respectively) in haemophilia A, and also for haemophilia B (85% versus 52%), but that the quality of the data was poor.

ESC noted that the pharmacokinetic data suggested considerable variation in the half-life between EHL products, and that this might have implications for negotiating the unit cost of different products.

ESC noted that the economic evaluation for prophylaxis consisted of a cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA), which evaluated cost per infusion avoided and cost per bleed avoided. ESC noted that as the evidence for on-demand and surgical prophylaxis usage was insufficient, a cost-minimisation model had been applied.

ESC noted that an alternative scenario using data from the study by Miners AH et al (2016) had been modelled alongside the base case which used data from the A-LONG study (Shapiro AD et al 2014). ESC noted that for haemophilia A, the CUA found:

- a wide range of ICER/QALY gain in different age groups, which were lower in the under 12 years age groups but high (~\$485,000) in the 18+ years age group in the base case analysis

- a much narrower range of ICER/QALY gain for the alternative scenario, ranging from ~\$42,000 to \$65,000
- ICER/QALY gain of ~\$326,500 in the lifetime model
- ICER/QALY gain of ~\$60,000 in the alternative scenario lifetime model.

ESC noted that results of the CEA showed a difference in lifetime costs between the base case and alternative scenarios:

- ICER per infusion avoided \$177; ICER per bleed avoided ~\$5,200 (base case)
- ICER per infusion avoided \$23; ICER per bleed avoided ~\$4,500 (alternative scenario).

ESC noted that for haemophilia B, results of the CUA found:

- factor IX was generally more cost-effective than factor VIII; for the older age groups (12–17 and 18+ years), EHL was dominant (less costly, more effective) and had an ICER/QALY gain ranging from ~\$48,800 to ~\$364,700 in the younger age groups
- factor IX was cost-effective, with an ICER/bleed avoided of up to \$2,107
- ICER/QALY gain of ~\$17,300 in the lifetime model.

ESC noted that results of the CEA showed that although there was a substantial decrease in the ICERs for infusions/bleeds avoided, the alternative scenario was dominant.

ESC noted that, for the haemophilia A model, the variation in the ICER across the age ranges was due to: changes in dosing patterns in the different age groups (affecting both costs and QALYs), changes in the relative bleeding rates (affecting both costs and QALYs) and changes in incremental costs per dose due to weight differences associated with age (affecting costs).

ESC noted that in contrast to the base case scenario, the ICERs per QALY gained in adults and adolescents were substantially lower in the alternative scenario over a one year time horizon. ESC noted that this was due to the data sources used, as the decrease in factor VIII consumption reported in the Miners study (17%), compared to a slight increase in factor VIII use, in the A-LONG study (Shapiro AD et al 2014). ESC noted the base case for the lifetime model was not cost-effective because of the relatively small reduction in factor consumption compared to the increase in price per IU modelled. ESC considered that consequently the model was based on an inappropriately small decrease in factor consumption.

ESC noted that, for the haemophilia B model, the incremental cost within each age group was observed to increase from \$4,000 to \$30,000 in children, while in adolescents and adults; EHL factor IX was estimated to be cost-saving. ESC noted that, as for haemophilia A, the main driver of incremental costs was the difference in factor consumption modelled, relative to the price increase. This resulted in a dramatic increase in ICER/QALY gain in the 6–11 age group, whereas dominant ICERs were observed in adults.

ESC considered that the interpretation of the ICERs was difficult as there was large variation depending on the age group modelled and the source data used to inform annualised doses of factor consumption and/or bleeding rates. ESC queried whether the trial results used in the economic model would be realised in practice.

ESC noted that three SHL factor VIII and factor IX products currently being used in Australia are assumed to be only those listed on the NBA Australia's National Product List. ESC noted that these products appeared to be considered interchangeable, with a weighted cost per IU for both groups derived from total IU issued of all products. ESC considered that

the aggregation of products with differing estimated annualised doses was inappropriate, potentially affecting costs and hence savings.

ESC noted that no evidence was identified to support the differential consumption of factor VIII and factor IX IU between SHL and EHL products in the on-demand and surgical prophylaxis indications. Therefore, the base case had assumed no difference in unit use between SHL and EHL for these indications, which may not have been accurate.

ESC noted that a treatment benefit as measured by reduction in annualised bleed rates (ABR) had not been converted into long-term outcomes (bleeding into joints, arthritis, and joint replacements) in the CUA. ESC considered that treatment benefit with EHL products had most likely been underestimated because:

- the long-term effect of bleeds on quality-of-life or medical costs, in terms of development of target joints and joint surgery, had not been modelled in the base case. ESC considered that this most likely underestimated the benefits of EHL products particularly for patients with haemophilia A who have three times the risk of arthroplasty compared to patients with haemophilia B
- the Markov model structure (two states; alive with haemophilia, and dead) used to evaluate lifetime costs and benefits was an oversimplification and did not capture the benefits of a reduction in bleeds
- a one-year time horizon used in the decision tree may have been too short to capture the benefits accrued from treatment with EHL.

ESC considered that as the simplistic structure Markov model removed potential health gains and savings from the ICER, the model would benefit from a revision to enable the capture of all health gains.

ESC noted that the baseline utility used in the haemophilia A model had been applied per year across the lifetime of the model, which ESC did not consider was an appropriate method. ESC also queried the methodology by which a visual analogue score derived from a study (Chowdary P et al 2016) estimating the benefits of switching treatments had been directly incorporated into the model for haemophilia B, affecting results. ESC considered that the correct method would have been to convert this into a utility score.

ESC noted that, as proposed prices per IU of EHL factors for use in Australia have not been published, the base case analysis for EHL factor VIII assumed a 20% increase in price relative to the price per IU of SHL factor VIII, and for EHL factor IX assumed a 100% increase in price of EHL factor IX relative to the price per IU of SHL factor IX, weighted by use. The results of both analyses once again showed that cost-effectiveness was highly sensitive to changes in relative factor consumption, based on the different data sources used.

ESC noted that the submission had included a literature review investigating price differentials for EHL products internationally to inform prices to be tested in the economic model. For factor VIII products, the increase in price of EHL relative to SHL ranged from 8–80%, and for factor IX, the increase in price ranged from 100–219%. However, ESC noted that modelling of the base case using these price ranges did not include consumables, or a potential decrease in the number of central venous access lines in children, both of which may decrease due to fewer infusions with EHL products.

ESC considered that the uncertainty in the supplier price made the model highly price-sensitive, and that there was potential for costs to blow out as cost per IU increased.

ESC noted that for on-demand and surgical prophylaxis, a range of the cost-minimisation price per IU for EHL factor VIII and factor IX in order to maintain equi-effectiveness was presented, based on the assumption of a 1:1 ratio of dose equivalence (in IU) for EHL:SHL. The cost-minimisation model found that equi-effective dosing would result in:

- prices ranging from \$redacted – \$redacted for factor VIII; and
- prices ranging from \$redacted – \$redacted for factor IX.

ESC noted that a market-based approach had been used to estimate the financial implications for the introduction of EHL factors for haemophilia treatment. ESC noted that the net cost for EHL factor VIII prophylaxis ranged from ~\$5.8 million to ~\$10.5 million per year over five years, with a net cost for EHL factor VIII on-demand ranging from ~\$7.3 million to ~\$13.3 million. ESC noted that the net cost for EHL factor IX prophylaxis ranged from \$19 to \$33 per year over five years, with a net cost for EHL factor IX on-demand ranging from ~\$4.5 million to ~\$7.8 million.

ESC noted that there was considerable uncertainty around the financial impacts based on the rate of uptake (60% in year 1, increasing to 95% in year 5), change in factor use (offsets) and price per IU.

ESC noted that the majority of patients with haemophilia were treated at specialist haemophilia treatment centres and that current prescribing and authorisation of SHL factor VIII and factor IX products is limited to haematologists, suggesting that this process was also suitable for EHL products and did not require changing.

ESC noted that there is an existing Australian Blood Disorders registry, provided through the NBA, which currently captures usage and outcomes in patients with haemophilia, and that there was the potential for this dataset to be enhanced over time to provide local data for future modelling.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)