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Assessment of extended half-life clotting factor concentrates

Final Report

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Research Team

Ms Skye Newton - Team Leader, Medical HTA

Ms Klara Salinger – Research Officer

Ms Leesa Pridham – Senior Research Officer

Ms Jacqueline (Jacci) Parsons – Team Leader, Special projects

Prof Tracy Merlin – Managing Director

Adelaide Health Technology Assessment (AHTA)

School of Public Health

University of Adelaide

Adelaide, South Australia

Conflicts of interest

The authors of this document have no financial or other conflicts of interest pertaining to clotting factors, or the conditions assessed.



Executive Summary

A systematic literature review was performed with the primary aim of determining whether extended half-life factor VIII and IX clotting concentrates were at least as safe and effective as standard half-life clotting factors, over and above pharmacokinetic parameters, for treating clotting disorders haemophilia A and B.

Haemophilia A

Seven extended half-life (EHL) factor VIII products were reviewed. The pharmacokinetic properties of BAX 855, BAY 94-9027, CSL 627, N8-GP and rFVIII-Fc were superior to those of standard half-life (SHL) products Advate and rFVIII-FS. BAY 81-8973 was marginally superior to rFVIII-FS. Human-cl rhFVIII was inferior to rFVIII-FS. In adults, the half-life was lengthened by about 50% while half-life extension in children was around 30% (derived from one study). Given the lack of comparative data in paediatric populations, this estimate must be taken with caution. Overall, FVIII product half-life tended to be greater in older children (aged 6 to 11 years) than in the younger subgroup (0 to 5 years). There was no evidence directly comparing one EHL factor against another.

The primary clinical outcome of interest was annualised bleeding rates (ABR). Four EHL products (BAY 81-8973, Human-ch rhFVIII, 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 27-82% the rates of those on SHL prophylaxis. An indirect comparison between BAY 81-8973 and rAHF-PFM and turoctocog alfa found that patients on BAY 81-8973 had smaller ABRs than those on turoctocog alfa and similar ABRs to rAHF-PFM. Overall, all trials restricted recruitment to patients with severe haemophilia only.

For those receiving prophylactic treatment, regimens could be changed as required by either increasing dose or decreasing interval. Some studies left changes to the discretion of the investigator- or there would be a specific limit before the patient would not qualify for the analysis set.

There was little information identified in the review on patient characteristics which would predict which dosing regimen would be more safe and effective for different patients. Von Willebrand factor antigen levels were found to be related to pharmacokinetic properties of EHL products. Other possible characteristics which were thought to influence bleeding risk included bleeding phenotype, joint status and patient activity level and blood type.

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 three in children- the majority being hypersensitivity. It is not fully known how many of these individuals withdrew from the studies. Only one individual developed inhibitors in the extension study to Pathfinder 2, this patient was withdrawn from the study. The applicability of these results to previously untreated patients or patients with inhibitors is unknown as trials in these populations are still underway.

With the exception of human cl-rFVIII (which should possibly not be classified as an EHL product), the EHL products examined, appeared as safe as SHL products, and more effective than SHL products, over and above pharmacokinetic parameters, for treating haemophilia A. The evidence was not considered to be strong, given the lack of direct comparison on clinical outcomes.

Overall, the quality of the evidence was considered to be very poor. Limitations include the lack of direct comparison on clinical outcomes; inconsistent use of the type of estimate (e.g. means and medians across studies); and lack of estimates of variance. The study populations across all studies was highly consistent in terms of disease severity and cut-offs for age.

Table 1 Summary of the benefits and harms of prophylaxis with EHL vs SHL factor VIII products for adolescents and adults with haemophilia A

Outcomes	Participants Studies	Quality of evidence	Results	Interpretation	GRADE
Annualised bleeding rate	N= 1016 K= 4 Historical control studies and a matched indirect comparison	Risk of bias: -1 Inconsistency:-1 Indirectness: 0 Imprecision: -1 Publication bias: 0	In patients who are on a prophylactic regimen, bleeds tended to reduce by about 4 per year with EHL products if they were previously on a prophylactic regimen and 30 bleeds a year if previous regimen was on-demand. The number of historical bleeds in each study varied between studies.	EHL products are marginally superior to SHL products on effectiveness outcomes.	⊕⊖⊖⊖
Pharmacokinetic outcomes	N = 186 K = 8 Interrupted time series without a parallel control group	Risk of bias: 0 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0	Discounting human-cl FVIII, EHL products were superior to SHL products. AUC was 20 to 80% times greater and T _{1/2} was 10-70% longer. Clearance was 15 to 40% times less and time to clotting factors was 50% greater. Mean trough levels showed a marked increase: between 2.9 to 4.7 times the levels of SHL factors. Overall, effect size was modest and there was some dose-response.	EHL products are detectable for much longer than SHL products-excluding human-cl rFVIII	⊕⊖⊖⊖
Quality of life	N= 170 K= 2 Before and after case series	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0	Most studies were not powered detect a significant difference between SHL and EHL products. No clinically significant difference between SHL and EHL was detected in prophylaxis patients.	EHL products may marginally improve QoL.	⊕⊖⊖⊖
Inhibitor development	N= 1339 K= 16 Case series	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	Only one instance of inhibitor formation. However, all trials were in previously-treated patients with no history of inhibitors. No trials directly compared the rate of inhibitor development in SHL and EHL products.	EHL products are as safe as SHL products in those without a history of inhibitors.	⊕⊕⊖⊖
Serious adverse events	N= 1339 K= 16 Case series	Risk of bias: 0 Inconsistency: 0	Three treatment-related serious adverse events	The rate of serious adverse	⊕⊕⊖⊖

Outcomes	Participants Studies	Quality of evidence	Results	Interpretation	GRADE
		Indirectness: 0 Imprecision: 0 Publication bias: 0	occurred. No trials directly compared the rate of adverse events in SHL and EHL products.	events due to EHL products is low (<1%).	

Table 2 Summary of benefits and harms of prophylaxis with EHL vs SHL factor VIII products for children with haemophilia A

Outcomes	Participants Studies	Quality of evidence	Results	Interpretation	GRADE
Annualised bleeding rate	N= 53 K= 1 Historical control studies and a matched indirect comparison	Risk of bias: -1 Inconsistency: N/A Indirectness: 0 Imprecision: -1 Publication bias: 0	In patients who are on a prophylactic regimen, bleeds tended to reduce by about 4 per year if they were previously on a prophylactic regimen and 50 bleeds a year if previous regimen was on-demand. The number of historical bleeds in each study varied between studies.	EHL products are marginally superior to SHL products on effectiveness outcomes.	⊕⊖⊖⊖
Pharmacokinetic outcomes	N = 57 K = 2 Interrupted time series without a parallel control group	Risk of bias: 0 Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias: 0	Discounting human-cl FVIII, EHL products were superior to SHL products. AUC was 40% greater and T _{1/2} was 25% longer. Clearance was 25% less. There was a serious lack of comparative pharmacokinetic data. Overall, effect size was marginal and there was some dose-response.	EHL products are detectable for longer (marginally) than SHL products-excluding human-cl rFVIII	⊕⊖⊖⊖
Quality of life	N= - K= -	Risk of bias: Inconsistency: Indirectness: Imprecision: Publication bias:	There were no estimates presented to suggest an improvement in QoL. Mullins et al. (2016) does claim a statistically significant difference in PedsQL score in Psychosocial and Physical health domains, but failed to produce any figures to back up claim.	EHL may increase QoL, but more research is required.	
Inhibitor development	N=455 K= 8 case series	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	There were no instances of inhibitor development.	EHL products are as safe as SHL products in those without a history of inhibitors.	⊕⊕⊖⊖
Serious adverse events	N= 455 K= 8 case series	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0	Seven treatment-related serious adverse events occurred. No trials directly compared the rate of adverse events in SHL	The rate of serious adverse events due to EHL products is low (<1%).	⊕⊕⊖⊖

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Haemophilia B

Three extended half-life (EHL) factor IX products which were reviewed. They were compared to standard half-life (SHL) factor IX products on pharmacokinetic parameters, and the effectiveness outcome of bleeding rates. Comparisons with baseline were made on clinical outcomes of target joint status and quality of life. There was a lack of direct comparisons of the safety of EHL products compared to SHL products, so high-level summaries of adverse events for both sets of products were compared.

The pharmacokinetic properties of N9-GP, rFIXFc and rIX-FP were superior to those of pdFIX and rFIX. There was no evidence directly comparing one type of EHL against another.

The primary clinical outcome of interest was annualised bleeding rates. All studies comparing prophylaxis with SHL FIX products (historical data) with prophylaxis with EHL FIX products (trial data), 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. All the trials were restricted to patients with moderately-severe to severe haemophilia B. It is therefore unknown to what extent the results are generalizable to moderate or mild haemophilia.

Two different styles of adjustment to prophylaxis were seen. Patients could either have their dose of prophylaxis adjusted up or down as required (based on pharmacokinetic outcomes, clinical outcomes, or physical activity level) or they could have their prophylactic interval adjusted. One trial used set cut-offs to determine if patients should be switched to dosing every 10 or 14 days, while another trial allowed individualised interval prophylaxis. This trial used a dose of 100 IU/kg, and extended the interval until the patients' FIX target trough level was between 1 and 3 IU/dL above baseline. Approximately half of patients had their prophylaxis interval adjusted to between 14 and 28 days. The rate of bleeding in this group was still marginally less than the historical data from patients receiving SHL products prophylactically.

Quality of life improvements were seen in groups of patients receiving EHL product prophylactically, particularly if they had been on an on-demand regimen prior to trial entry.

Real world data showed that adherence to treatment regimens was considerably higher when patients were on a treatment regimen with EHL products rather than SHL products.

There were no data to suggest that EHL products are associated with a higher rate of adverse events than SHL products. No inhibitors developed in patients without a history of inhibitor development to SHL FIX products. Two patients had severe adverse events due to EHL products, one of whom was medically treated and remained on the EHL product, the other who stopped EHL treatment, and recovered fully within hours. The applicability of these results to previously untreated patients is unknown.

Limitations of the data were that all the trials were in those with moderately-severe to severe haemophilia B, previously treated patients, with no history of inhibitors. The safety and effectiveness of EHL products outside of this population is therefore unknown.

A summary of the benefits and harms of EHL versus SHL factor IX products for adolescents and adults is shown in Table 3.

Table 3 Summary of the benefits and harms of prophylaxis with EHL vs SHL factor IX products for adolescents and adults with haemophilia B

Outcomes	Participants Studies	Quality of evidence	Results	Interpretation	GRADE
Annualised bleeding rate	N = 125 K = 4 historical control studies	Risk of bias: -1 Inconsistency: -1 Indirectness: 0 Imprecision: 0 Publication bias:0	EHL products reduced the median number of bleeds by approximately 2 bleeds per year. The number of historical bleeds in each study varied between studies.	EHL products are superior to SHL products on effectiveness outcomes	⊕⊕⊖⊖
Pharmacokinetic outcomes	N = 51 K = 3 interrupted time series without a parallel control group	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias: 0	EHL clearly superior to SHL products with AUC 6 to 10 times greater, T _{1/2} 2 to 6 times longer, clearance 1/10 to 1/2 that of SHL, and time to particular clotting factor thresholds over twice as long. There was a trend favouring EHL products on IR. Effect sizes were large, and there were dose response gradients.	EHL products are detectable in the blood for much longer than SHL products.	⊕⊕⊖⊖ to ⊕⊕⊕⊕
Quality of life	N = 82 K = 3 before and after case series	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias:0	Approximately half of patients swapping from SHL to EHL prophylaxis had clinically meaningful changes on HR-QOL questionnaires.	EHL products can improve QOL	⊕⊕⊖⊖
Inhibitor development	N = 397 K = 10 case series	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias:0	The inclusion criteria in the published trials restricted participation to those patients, without a history of inhibitors. In this group of patients, no inhibitors were identified due to EHL FIX products.	EHL products are as safe as SHL products	⊕⊕⊖⊖
Serious adverse events	N = 443 K = 12 case series	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias:0	2/443 patients had serious adverse events attributable to an EHL product (allergic reaction and haematuria). No trials directly compared the rate of adverse events in SHL and EHL products.	The rate of serious adverse events due to EHL products is low (<1%)	⊕⊕⊖⊖
Adherence	N = not stated K = 2 retrospective cohort studies	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias:0	Data from health insurance companies and pharmacies showed that adherence to dosing regimens with EHL products was considerably higher than with SHL products.	Patients accept EHL product treatment regimens.	⊕⊕⊖⊖

Table 4 Summary of the benefits and harms of prophylaxis with EHL vs SHL factor IX products for children with haemophilia B

Outcomes	Participants Studies	Quality of evidence	Results	Interpretation	GRADE
Annualised	N = 46	Risk of bias: 0	Overall trend showing reduced	Samples too	⊕⊖⊖⊖

Outcomes	Participants Studies	Quality of evidence	Results	Interpretation	GRADE
bleeding rate	K = 2 historical control studies	Inconsistency: -1 Indirectness: 0 Imprecision: -1 Publication bias:0	bleeding rates, but one subgroup showed an increase in bleeding. This inconsistency may be due to small numbers.	small to make strong conclusions.	
Pharmacokinetic outcomes	N = 17 K = 1 interrupted time series	Risk of bias: 0 Inconsistency: N/A Indirectness: -1 Imprecision: 0 Publication bias:0	EHL products clearly superior to SHL products on pharmacokinetic outcomes such as AUC, terminal half-life and clearance.	EHL FIX products stay in the blood much longer than SHL FIX products	⊕⊕⊕⊖ Rated up due to very large effect sizes
Quality of life	N = 0 K = 0				
Inhibitor development	N = 52 K = 2 case series	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias:0	No FIX inhibitors developed in those specifically chosen for trials due to no history of FIX inhibitors, despite exposure to FIX products	No signs that EHL products are more likely than EHL products to cause FIX inhibitor development.	⊕⊖⊖⊖
Serious adverse events	N = 82 K = 3 case series	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Publication bias:0	No serious adverse events considered related to EHL products	Tentative conclusions due to small trials, that EHL products appear safe	⊕⊖⊖⊖
Adherence	N = not stated K = 1 retrospective cohort study	Risk of bias: -1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias:0	20% increase in adherence with EHL products compared to SHL products, based on U.S. Insurance data	Adherence is higher in EHL products than SHL products, which is likely a reflection of patient/parent acceptance	⊕⊖⊖⊖