Incremental Cost of Switching to Extended Half-life (EHL) Coagulation Factor Products to Treat Hemophilia Among 15 Million Commercially Insured Members

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Background

- Extended half-life (EHL) recombinant (r) coagulation factor (F) products recently approved by the Food and Drug Administration (FDA) include:
  - For hemophilia A, an Fc fusion protein, rFVIII (Eloctate®), a pegylated rFVIII (Adynovate®), and a single chain rFVIII (Afstyla®).
  - For hemophilia B, an Fc fusion protein, rFIX (Alprolix®) and an albumin fusion protein rFIX (Idelvion®). In addition, a glycopegylated, rFIX (Rebinyn®) was approved in May 2017, launched in February 2018.
- Coagulation factor product half-life:
  - Conventional, standard half-life (SHL) FVIII products have a mean adult half-life of 12 hours and typical prophylaxis is every other day or every third day. However, there is considerable variation between individuals; half-life ranged between six hours and 25 hours in two large studies of pediatric and adult patients.[1]
  - Conventional, SHL FIX products have an average half-life of about 25 hours and typical prophylaxis is twice per week.
  - EHL FVIII products have led to substantial half-life extension in some patients, but the average extension is only about one and a half times a patient's baseline, SHL half-life, or about an additional six hours on average.[2]
  - In contrast, EHL FIX products have demonstrated an average extension of about four times the average half-life of SHL FIX products.[2]
- Prophylaxis, the regular administration of coagulation factor products to prevent bleeding, is the standard of care for persons with severe hemophilia A or B, defined as factor (F) VIII or FIX levels less than 1%. The recommended aim of prophylactic therapy is to keep trough levels between doses of FVIII or FIX greater than 1%.[3] Persons with moderate hemophilia A or B, defined as FVIII or FIX levels greater than 1% to 5% are usually treated with coagulation factor products "on demand" to stop bleeding, rather than with prophylaxis.
- An analysis was recently reported of a national database of patients from 138 hemophilia treatment centers affiliated with American Thrombosis and Hemostasis Network (ATHN).[4] Prescribed treatment was determined for all patients with moderate or severe hemophilia A or B without active inhibitors as of June 2016 (baseline) and March 2017 (nine months later). This study found:
  - In March 2017, 63% of hemophilia A and 39% of hemophilia B patients were prescribed prophylaxis.
  - The proportion of hemophilia A patients prescribed an EHL FVIII increased from 13% at baseline to 21% nine months later.
  - The proportion of hemophilia B patients prescribed an EHL FIX increased from 30% at baseline to 42% nine months later.
  - Reported results did not include: what was dispensed to these patients; how much and how frequently the products were self-administered; or the costs and changes in costs resulting from uptake of EHL products.
- Administrative claims data lack information about severity of hemophilia, prescribed dosing, or administration dates and quantities administered. However, claims data can precisely quantify timing, quantities and costs of products dispensed.

Objective

- To determine, in a large commercially insured population:
  1) Total numbers of members with hemophilia A and B treated with factor products by time intervals;
  2) Percentage of members using EHL products by time intervals; and
  3) Change in number of factor units billed and cost for individual members switching from SHL to EHL products.

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Methods

- Complete pharmacy and medical claims from January 2013 to July 2017 from a population averaging 15 million members per month were queried to identify all pharmacy and medical claims for a hemophilia product, defined as any FVIII, FIX, or FVIII/von Willebrand (vWF) complex, or the bypassing products activated prothrombin complex (FEIBA®) and rFVIIa (NovoSeven®).
- Diagnosis codes from all medical claims for any service, factor claims, and member's gender were used to assign members with factor claims to hemophilia A, hemophilia B, symptomatic hemophilia carrier, vWD, or other/unassigned indication categories.
- Utilizers per 100,000 member-years and claims cost per member per month (PMPM) were calculated by categories by six-month intervals.
- All members switching from a SHL rFVIII or rFIX to a EHL who had at least 180 days of continuous eligibility before and 210 days after first EHL claim were studied to determine their factor cost and units before and after switch, described as rates per six months.
  - Pre-switch SHL expense and units were summed for claims incurred between the first EHL claim date and the later of the first EHL date minus 365 days or first date of continuous eligibility preceding first EHL date.
  - Post-switch EHL expense and units were summed for claims incurred between the first EHL claim date plus 30 days and the later of last date of continuous eligibility or June 30, 2017.
  - Members were excluded if they had no SHL claim in the pre-, no EHL in the post-, or any SHL claim in the post-period.
- All diagnosis codes on medical claims incurred by switching study members were evaluated for evidence of bleeding events.
- Costs described are allowed amounts, sum of plan and member paid, without adjustment for patient assistance programs coupons.
- Annualized pre-switch (medical) total cost of care, non-factor and annualized post-switch (medical) total cost of care, non-factor was calculated.

Results

- **Table 1** shows the number of members with any hemophilia product claim by indication by six-month intervals from January 2013 to June 2017. The average number of members per 100,000 using hemophilia products per six months across all periods studied was 3.54 hemophilia A and 0.95 hemophilia B.
- **Table 2a** shows the percentage of hemophilia A members with a hemophilia product claim by product category (plasma-derived FVIII, rFVIII SHL, rFVIII EHL, FVIII/vWF complex, or bypassing product) by six-month intervals from January 2013 to June 2017. **Figure 1a** shows hemophilia product claims expense PMPM for these members.
  - Use of rFVIII EHL products:
    - First appeared in June 2014, following FDA approval of Eloctate®.
    - Increased to 13.8% in the period 1H2016 (January 2016 to June 2016) and 21.4% of hemophilia A users in the period 1H2017 (January 2017 to June 2017).
    - Appears to account for most of the increase in cost for hemophilia products for hemophilia A in 1H2017.
  - Most of the small percentage of hemophilia A members with claims for FVIII/vWF complex or bypassing products had very high expense for these products and were, presumably, undergoing immune tolerance induction or treatment for a high titer inhibitor, respectively.
- **Table 2b** shows the percentage of hemophilia B members with a hemophilia product claim by product category (plasma-derived FIX, rFIX SHL, rFIX EHL, or bypassing product) by six-month intervals from January 2013 to June 2017 . **Figure 1b** shows hemophilia product claims expense PMPM for these members.
  - Use of rFIX EHL products:
    - First appeared in April 2014, following FDA approval of Alprolix®.
    - Increased to 21.4% in the period January 2016 to June 2016 and of 39.9% of hemophilia B users in the period 1H2017.
    - Appears to account for most of the increase in cost for hemophilia products for hemophilia B in the most recent three years.
  - Most of the very small percentage of hemophilia B members with claims for bypassing products had very high expense for these products and were, presumably, being treated for a high titer inhibitor.
- There were 34 hemophilia A and 20 hemophilia B members who switched from a SHL to an EHL product and met study inclusion criteria. **Table 3** illustrates methods and results for one hemophilia A member. **Table 4** summarizes findings:
  - For the 34 hemophilia A members, mean SHL cost in the pre-switch period was $127,168 per six months compared with $300,429 (2.36 times higher) for EHL in the post-switch period; mean SHL units were 115,424 per six months compared with 167,282 for EHL (45% higher).
  - For the 20 hemophilia B members, mean SHL cost was $116,909 per six months in the pre-switch period compared with $230,209 (1.97 times higher) for EHL in the post-switch period; mean SHL units were 104,637 per six months compared with 85,745 for EHL (18% lower).
  - None of the 54 switching members had any claim indicating a bleeding event before or after switching.

Limitations

- Due to the rarity of severe hemophilia A and B, frequent disenrollment and new enrollment of commercially insured members, and how recently EHL product use has expanded, only a small sample of members could be followed longitudinally for at least six months before and after switching to an EHL product.
- Possible changes in adherence to therapy could not be assessed because administrative claims lack information about prescribed dosing and timing of doses administered.
- Bleeding events in hemophilia usually do not result in medical claims with diagnosis codes indicating bleeding. Detailed logging of bleeding events by patients or their caregivers may be necessary to document changes in the incidence of bleeding events after switching to EHL.
- The data lack sufficient information about member management to access utilization and costs by hemophilia treatment center (HTC) management versus non-HTC management.

Conclusions

- In this real-world data analysis using integrated medical and pharmacy claims data, members converting to EHL factor products for both hemophilia A and B were associated with substantially higher costs. The clinical value of the doubling in cost will need to be justified.
- Although we found no differences in bleeding events or total cost of care, excluding non-factor medical costs, among members switching from SHL to EHL factor products, medical claims data would only identify the most severe bleeding events. Patient daily logs would be needed to assess less severe bleeding events.
- We found members switching to a hemophilia B EHL factor IX product was associated with a decrease in average number of units dispensed, consistent with less frequent dosing in practice. In contrast, switching to a hemophilia A EHL factor VIII product was associated with an increase in average number of units dispensed. The expectation was that there would be a decrease in cumulative units utilized due to increased dosing interval or decreased breakthrough bleeds.
- In the 15 million commercially insured members assessed, EHL factor IX products have had relatively more uptake, at 40%, than EHL FVIII products at 21%, but the latter are being used by more members due to the higher prevalence of hemophilia A.
- Because four in five hemophilia A members still are using a SHL product, there is substantial risk for many more EHL conversions with an anticipated more than doubling in cost, at an additional $300,000 per year cost per EHL treated member. Pharmacy benefit managers and health plans will need to closely assess EHL cost effectiveness.

Table 1. Members with any Hemophilia Product Claim by Indication, Over 4.5 Years

	Members with a hemophilia product claim[†]									
Indication*	1H2013	2H2013	1H2014	2H2014	1H2015	2H2015	1H2016	2H2016	1H2017	Average
Hemophilia A	425	489	510	519	575	561	521	537	538	519
Hemophilia B	117	116	149	142	160	159	129	142	138	139
von Willebrand's disease	70	79	78	100	105	97	103	114	100	94
Hemophilia symptomatic carrier	27	37	18	32	47	27	19	19	15	27
	Members per 100,000 with a hemophilia product claim[†]									
Indication*	1H2013	2H2013	1H2014	2H2014	1H2015	2H2015	1H2016	2H2016	1H2017	Average
Hemophilia A	3.09	3.53	3.44	3.39	3.66	3.67	3.55	3.78	3.70	3.54
Hemophilia B	0.85	0.84	1.01	0.93	1.02	1.04	0.88	1.00	0.95	0.95
von Willebrand's disease	0.51	0.57	0.53	0.65	0.67	0.63	0.70	0.80	0.69	0.64
Hemophilia symptomatic carrier	0.20	0.27	0.12	0.21	0.30	0.18	0.13	0.13	0.10	0.18

H = half of year, for example, 1H2013 is Jan. 1, 2013 through June 30, 2013
*Indication was deduced from diagnosis codes on all medical claims, factor products dispensed, and patient's gender; hemophilia product = any FVIII, FIX, FVIII/vWF or bypassing product
†From a commercially insured population of approximately 15 million members per year

Figures 1a and 1b. Hemophilia Product Claims Expense Per Member Per Month (PMPM), Over 4.5 Years

Figure 1a. Hemophilia A*

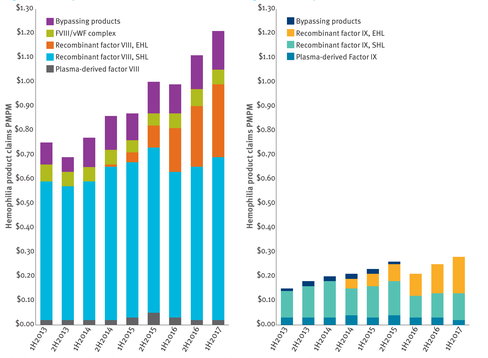

Figure 1b. Hemophilia B*

*Indication was deduced from diagnosis codes on all medical claims, factor products dispensed and patient's gender.
PMPM = per member per month; vWF = von Willebrand Factor; EHL = extended half-life; SHL = standard half-life;
H = half of year, for example, 1H2013 is Jan. 1, 2013 through June 30, 2013
Note: Denominators for PMPM are all member months eligible for medical + pharmacy benefits in each six-month interval.

References

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Tables 2a and 2b. Percentage of Hemophilia Members with a Hemophilia Product Claim by Product Category, Over 4.5 Years

Table 2a

	Hemophilia A members — percent with a hemophilia product claim*								
Hemophilia A product	1H2013	2H2013	1H2014	2H2014	1H2015	2H2015	1H2016	2H2016	1H2017
Plasma-derived factor VIII	5.2%	6.1%	7.3%	6.7%	11.1%	6.8%	5.4%	3.4%	2.6%
Recombinant factor VIII, SHL	89.9%	89.2%	88.8%	88.6%	82.6%	83.4%	78.1%	74.9%	72.9%
Recombinant factor VIII, EHL	0.0%	0.0%	0.0%	1.9%	5.2%	8.0%	13.8%	16.4%	21.4%
FVIII/vWF complex	2.8%	3.3%	3.3%	2.7%	3.5%	2.7%	4.6%	4.7%	3.9%
Bypassing products	4.2%	5.1%	4.1%	4.0%	3.7%	4.1%	4.4%	4.1%	3.9%

Table 2b

	Hemophilia B members — percent with a hemophilia product claim*								
Hemophilia B product	1H2013	2H2013	1H2014	2H2014	1H2015	2H2015	1H2016	2H2016	1H2017
Plasma-derived factor IX	29.1%	25.0%	23.5%	18.3%	19.4%	19.5%	17.1%	19.7%	13.8%
Recombinant factor IX, SHL	72.6%	75.9%	76.5%	73.2%	65.6%	63.5%	56.6%	57.0%	53.6%
Recombinant factor IX, EHL	0.0%	0.0%	3.4%	12.0%	19.4%	20.8%	29.5%	29.6%	39.9%
Bypassing products	2.6%	2.6%	2.7%	1.4%	1.3%	1.3%	1.6%	1.4%	0.0%

H = half of year, for example, 1H2013 is Jan. 1, 2013 through June 30, 2013; SHL = standard half-life; EHL = extended half-life
*Indication was deduced from diagnosis codes on all medical claims, factor products dispensed and patient's gender.

Table 3. Illustration of Method and Results for One Hemophilia A Member Who Switched to an Extended Half-life (EHL) Product

Claim#	Claim date	Days from previous claim	Interval*	Claim cost	Claim units	Factor VIII product category: SHL or EHL
1	10/21/14	Not Applicable	Pre	$24,268	25,545	Advate®, SHL
2	12/01/14	41	Pre	$23,655	24,900	Advate®, SHL
3	01/23/15	53	Pre	$23,406	24,900	Advate®, SHL
4	03/18/15	54	Pre	$23,649	25,158	Advate®, SHL
5	05/06/15	49	Pre	$24,012	25,545	Advate®, SHL
6	06/18/15	43	Pre	$12,685	13,495	Advate®, SHL
7	06/29/15	11	Pre	$10,357	11,018	Advate®, SHL
8	08/06/15	38	Pre	$11,128	11,018	Advate®, SHL
9	09/24/15	49		$51,215	32,830	Eloctate®, EHL
10	11/30/15	67	Post	$51,543	32,830	Eloctate®, EHL
11	02/03/16	65	Post	$51,839	33,230	Eloctate®, EHL
12	03/18/16	44	Post	$51,839	33,230	Eloctate®, EHL
13	05/10/16	53	Post	$52,171	33,230	Eloctate®, EHL
14	06/22/16	43	Post	$52,909	33,700	Eloctate®, EHL
15	08/18/16	57	Post	$49,694	31,652	Eloctate®, EHL
16	10/03/16	46	Post	$47,854	30,480	Eloctate®, EHL
17	11/28/16	56	Post	$52,572	33,700	Eloctate®, EHL
18	12/28/16	30	Post	$51,215	32,830	Eloctate®, EHL

*This member filled the first FVIII EHL claim on Sept. 24, 2015. The member was continuously eligible in the 365 preceding days through Dec. 31, 2016. The pre-period was defined the 365 days prior to the first EHL claim (Sept. 24, 2014 to Sept. 23, 2015). There was then a 30-day transition period, beginning with the first EHL claim. The post period began Oct. 24, 2015 and ran to the end of the analysis period Dec. 31, 2016 (434 days).
Cost = allowed amount (actual amount paid provider by plan and member); Units = international units of FVIII billed
The sums of FVIII cost and billed units were determined for the pre- and post-periods then standardized to rates per six months.

Interval*	Claim cost	Claim units	Factor VIII product
Pre-period 365 days	$153,160	161,579	Advate®, SHL
Post-period 434 days	$461,635	294,882	Eloctate®, EHL
Pre per 6 months	$76,580	80,790	Advate®, SHL
Post per 6 months	$194,121	124,000	Eloctate®, EHL
Ratio post/pre	2.53	1.53	Eloctate®, EHL / Advate®, SHL

Table 4. Total Cost of Care, Factor Utilization and Factor Cost for Members Switching from Standard Half-life (SHL) to Extended Half-life (EHL) Products

	Hemophilia A	Hemophilia B
Final analysis members*	34	20
Pre switch mean cost SHL per 30 days (annualized)	$21,200 ($254,000)	$19,200 ($230,000)
Post switch mean cost EHL per 30 days (annualized)	$50,000 ($600,000) 2.4x higher	$37,800 ($454,000) 2x higher
Pre switch mean units per 30 days SHL	19,000	20,000
Post switch mean units per 30 days EHL	28,000	16,000
Ratio of EHL to SHL cost	2.36	1.97
Annualized pre switch total cost of care (medical) non-factor	$4,420	$1,950
Annualized post switch total cost of care (medical) non-factor	$8,410	$1,940

*All members switching from a SHL rFVIII or rFIX to an EHL who had at least 180 days of continuous eligibility before and 210 days after first EHL claim were studied to determine their factor cost and units before and after switch, described as rates per six months. Pre-switch SHL expense and units were summed for claims incurred between the first EHL claim date and the later of the first EHL date minus 365 days or first date of continuous eligibility preceding first EHL date. Post-switch EHL expense and units were summed for claims incurred between the first EHL claim date plus 30 days and the later of last date of continuous eligibility or June 30, 2017. Members were excluded if they had no SHL claim in the pre-, no EHL in the post-, or any SHL claim in the post-period.

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