Real-World Analysis of Dispensed IUs of Coagulation Factor IX and Resultant Expenditures in Hemophilia B Patients Receiving Standard Half-Life Versus Extended Half-Life Products and Those Switching from Standard Half-Life to Extended Half-Life Products

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ABSTRACT

BACKGROUND: Hemophilia B requires replacement therapy with factor IX (FIX) coagulation products to treat and prevent bleeding episodes. A recently introduced extended half-life (EHL) recombinant FIX replacement product provided the opportunity to compare the amount of dispensed factor and expenditures for EHL treatment compared with a standard half-life (SHL) product.

OBJECTIVE: To determine factor international units (IUs) dispensed and expenditures associated with switching from nonacog alfa, the most commonly used SHL replacement product, to eftrenonacog alfa, an EHL FIX replacement product.

METHODS: Two U.S. claims databases were analyzed. A large national specialty pharmacy dispensation claims database was used to identify the number of IUs dispensed and monthly charges for all patients with hemophilia B from April 2015 to June 2016. Truven Health MarketScan Research Databases (January 2010–July 2016) were used to identify IUs and expenditures for patients with claims data for at least 3 months before and after switching from the SHL to the EHL product. Medians for IUs and expenditures are presented to accommodate for skewness of data distribution.

RESULTS: The national specialty pharmacy database analysis included 296 patients with moderate or severe hemophilia B (233 on SHL; 94 on EHL). Median monthly factor dispensed was 11% lower (2,142 IU) in the EHL versus SHL cohort over the study period, while individual monthly reductions ranged from 32% to 47% (9,838 IU to 16,514 IU). Using the wholesale acquisition cost, the median per-patient monthly factor expenditures over the 15-month study period were 94% higher (\$23,005) for the EHL than for the SHL product. Individual median monthly expenditure differences ranged from 15% (\$6,562) to 49% (\$19,624). In the Truven database, 14 patients switched from the SHL to the EHL product. The amount of factor dispensed was variable; in the 1-year period before and after the switch from the SHL to the EHL product, mean IUs dispensed decreased by 3,005 IU, while median IUs dispensed increased by 4,775 IU. Factor replacement expenditures were higher after switching from the SHL to the EHL product in each of the 3-month periods examined before versus after the switch.

CONCLUSIONS: This analysis of real-world data showed that switching from the SHL to the EHL product was associated with higher expenditures. Increased expenditures noted in the first 3 months after switching may be related to initial stocking up of the EHL product, but expenditures were sustained throughout the 1-year period of data analysis. Further analysis of these findings with larger numbers of patients should be explored.

J Manag Care Spec Pharm. 2018;24(7):643-53

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What is already known about this subject

- The standard of care for the treatment and prevention of bleeding events in patients with hemophilia B is replacement of factor IX (FIX) with plasma-derived or recombinant FIX (rFIX) clotting factor concentrates.
- Total weekly dosing with a conjugated extended half-life (EHL) rFIX product is approximately half that of a standard half-life (SHL) rFIX product.
- EHL products were priced to create parity with SHL products on an annual expenditure on factor replacement therapy basis as demonstrated in their respective clinical studies.

What this study adds

- In these analyses of real-world data, expenditures on EHL rFIX products were higher compared with those for SHL products, based on wholesale acquisition cost values and claims cost data.
- Higher expenditures were driven in part by greater-than-expected actual EHL product dispensed compared with published EHL product dosing.
- Additional real-world experience is needed to better understand EHL product dosing regimens and patient behavior.

Hemophilia B is caused by a mutation of the gene for factor IX (FIX), leading to a deficiency in the activity of coagulation FIX, which is part of the intrinsic coagulation pathway.^{1,2} Hemophilia B represents 15%-20% of all hemophilia cases and occurs in approximately 1 in 30,000 live male births across all racial and ethnic groups.^{1,2} Deficiency of FIX leads to reduced activity of the tenase complex and affects the ability to generate thrombin, which is essential to the formation and maintenance of a stable clot. The level of FIX coagulant activity determines the degree of bleeding tendency (normal FIX activity, 100% ± 50%), which is classified as mild (5%-40%), moderate (1%-5%), or severe (<1%).³ Severe FIX deficiency is characterized by spontaneous or trauma-induced

bleeding into soft tissue, muscle, or joints, and without optimal treatment, chronic pain, disability, and a reduced quality of life.^{1,2} The standard of care for the treatment and prevention of bleeding events and their complications centers on replacement of FIX with plasma-derived or recombinant FIX clotting factor concentrates.¹ In the United States, clotting factor availability is not constrained and patients use factor at home, as needed, and reorder to maintain an appropriate in-home inventory.

Recombinant-based clotting factor concentrate replacement products have evolved since the 1980s, when the plasma-derived products were shown to be associated with the transmission of hepatitis B and C viruses and human immunodeficiency virus.⁴ Cloning of the *FIX* gene allowed for use of recombinant technology to reduce the risk of infectious transmission from plasma-derived replacement products.^{2,5} The first recombinant FIX (rFIX) product was nonacog alfa (BeneFIX, Pfizer),⁶ which is structurally and functionally similar to endogenous FIX.² With longer pharmacokinetic sampling (up to 96 hours), the half-life of nonacog alfa was determined to be approximately 40 hours.⁷ A new product, eftrenonacog alfa (Alprolix, Biogen),⁸ was developed by covalently fusing a single molecule of rFIX to the dimeric Fc domain of immunoglobulin G to prolong the half-life.⁹ This product has a half-life 3 to 6 times longer than that of native or standard half-life (SHL) rFIX products.¹⁰ When introduced, the conjugated extended half-life (EHL) rFIX treatment was priced at parity with SHL products by balancing the lower expected international unit (IU) dispensed factor with the higher per-unit price and similar efficacy, based on annualized bleeding rates, as demonstrated in clinical studies.^{9,11,12}

The objectives of this analysis were to provide profiles of factor IUs dispensed and expenditures for an SHL product (nonacog alfa) versus an EHL product (eftrenonacog alfa) on a population level of specialty pharmacy claims and on a patient level for patients whose switch from the SHL to EHL product could be tracked in an administrative claims database at the individual patient level.

Methods

Study Design

This retrospective cohort study compared male patients with hemophilia B who were using either of the SHL or EHL rFIX replacement products. De-identified claims data were obtained from 2 sources to assess IUs dispensed and expenditures for overall rFIX replacement products (population-level analysis) and for those specifically switched from an SHL to an EHL product (patient-level analysis). Data were collected for individuals on nonacog alfa (the most commonly used SHL replace-

ment product) and eftrenonacog alfa (the only EHL product with data available during this period).

Population-Level Analysis

A large national specialty pharmacy dispensation claims database was used to identify monthly IUs dispensed and charges for all patients with moderate (FIX level 1%-5%) or severe (FIX level <1%) hemophilia B (diagnosis code of *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] 286.1 or *Tenth Revision* [ICD-10-CM] D67) from April 2015 to June 2016. The variables available in the national specialty pharmacy database were limited to details on the factor replacement product prescription, including date of shipment, factor and units dispensed, age (or year of birth), payer name, and physician location. However, factor replacement product regimen and severity of hemophilia B, items not available in traditional claims data, were self-reported patient data fields in the database and were used. The analysis reports differences between groups and does not provide data on patients who switched from 1 therapy to another.

Patient-Level Analysis

The Truven Health MarketScan Research Databases were used to identify claims from January 2010 to July 2016 (data range selected to permit the largest number of patients to be analyzed over time) for patients who had a diagnosis code for hemophilia B (using the same ICD criteria as above), a prescription for an EHL factor replacement product, a prior prescription for an SHL factor replacement product, and claims data for at least 3 months before and 3 months after switching from an SHL to an EHL product. For the patient-level analysis, the patient needed to have 1 quarter worth of enrollment/claims data before and after the switch from an SHL to an EHL product; individuals who did not have 90 days of follow-up for the quarter were not included. Switching was determined by the fact that subsequent claims in the database were no longer from the SHL product but from the EHL product.

This database provides detailed data of IUs dispensed and expenditures for both inpatient and outpatient health care services for approximately 100 million privately insured members (employees, dependents, and retirees) in the United States with primary or Medicare supplemental coverage through a variety of health plans, including fee-for-service, point-of-service, and capitation. Eftrenonacog alfa was first used in June 2014. Successive 3-month intervals (1-3, 4-6, 7-9, and 10-12 months) immediately before and after the switch were evaluated.

Assessments

The key outcome measures were IUs of factor dispensed and direct expenditures for the rFIX replacement products. Overall

FIGURE 1 Median and Mean Monthly Factor IUs Dispensed and Expenditures Associated with a Standard Half-Life (Nonacog Alfa) and with an Extended Half-Life (Eftrenonacog Alfa) Recombinant Factor IX Replacement Product^a

Note: Expenditures are based on 2015 dollars.

^aNational Specialty Pharmacy Database.

EHL=extended half-life; IUs=international units; SHL=standard half-life.

expenditures from the national specialty pharmacy database were calculated per patient per month (PPPM), consistent with the monthly updates provided. Wholesale acquisition cost (WAC) prices for 2015, provided by AnalySource (<http://classic.analysource.com/?switchsite=Y>), were used to calculate expenditures (nonacog alfa=\$1.30/IU; eftrenonacog alfa=\$2.85/IU). The WAC was used because it is the most commonly used benchmark in pharmacy purchasing of drugs, and many pharmacies procure their drugs through the wholesaler channel. Average expenditures PPPM while on the SHL or the EHL product (as determined by product class for which the insurance claim was submitted) were calculated by summing all available monthly data and dividing by the number of months from the first to the last month in which factor shipment occurred.

For the patient-level analysis using Truven data, expenditures were measured over 3-month (quarterly) periods, centered on the time of the patient's switch, as defined by the first month that an EHL claim was paid. Incomplete quarters (indi-

viduals who did not have 90 days of follow-up for the quarter) were not included. Expenditures (usually a medical benefit) were calculated using the Truven variable that measures gross payments to a provider for a service in which payment equals the amount eligible for payment under the medical plan terms after applying rules, such as discounts, but before applying coordination of benefits, copayments, and deductibles. Average quarterly expenditures and IUs dispensed before and after the switch were calculated using the quarters with data available.

All data were summarized descriptively. Median values (and their corresponding interquartile ranges [IQRs]) are provided to characterize the distribution of IUs dispensed and expenditures. These values are more robust owing to the presence of outliers, which are common in data for dispensed IUs and expenditures. Analyses were completed using SAS software package 9.4 (SAS Institute, Cary, NC) on Red Hat Enterprise Linux (Red Hat, Raleigh, NC).

TABLE 1 Population-Level Analysis of Average Monthly IUs of Factor Dispensed and Expenditures of Recombinant Factor IX Replacement Products^a

Parameter	Prophylaxis Patients		Episodic Treatment On-Demand Patients		All Patients	
	IUs Dispensed	Expenditures, \$	IUs Dispensed	Expenditures, \$	IUs Dispensed	Expenditures, \$
EHL cohort, n	83		10		94 ^b	
Median	16,939	48,276	14,364	40,936	16,638	47,419
IQR	10,283-26,428	29,308-75,319	12,968-27,817	36,959-79,279	10,486-27,017	29,886-76,999
Mean (SD)	20,516 (14,495)	58,469 (41,309)	22,630 (16,770)	64,495 (47,795)	20,703 (14,596)	59,003 (41,598)
SHL cohort, n	118		115		233	
Median	27,469	35,710	12,450	16,185	18,780	24,414
IQR	16,151-44,061	20,996-57,280	5,271-28,290	6,853-36,777	9,725-34,387	12,643-44,703
Mean (SD)	37,409 (40,908)	48,631 (53,180)	20,974 (25,778)	27,267 (33,511)	29,402 (35,262)	38,223 (45,841)
Difference in median IUs/dispensed expenditures, \$ (EHL-SHL product)	↓ 10,530	↑ 12,566	↑ 1,914	↑ 24,751	↓ 2,142	↑ 23,005
Median IUs dispensed/expenditures difference, % (EHL-SHL product)	↓ 38	↑ 35	↑ 15	↑ 153	↓ 11	↑ 94

Note: Data presented for the SHL product are specifically for nonacog alfa, and data presented for the EHL product are specifically for eftrenonacog alfa.

^aNational Specialty Pharmacy Database, N=296.

^bOne patient did not have data for a regimen (prophylaxis or on-demand) and was excluded.

EHL=extended half-life; IQR=interquartile range; IUs=international units; SD=standard deviation; SHL=standard half-life.

Results

Analysis of the National Specialty Pharmacy Database (Population-Level View)

Monthly IUs dispensed and expenditures were analyzed for 296 patients identified as having moderate or severe hemophilia B. In total, 233 patients received the SHL product and 94 received the EHL product during the 15-month study period. Some of these patients received both the SHL and EHL products over the study period. The majority of patients received rFIX replacement as a prophylactic regimen (57.8%), and 41.2% received rFIX replacement as episodic on-demand treatment. Overall, 80% of the patients were <40 years of age, and 63% of patients had their disease reported as severe. Median values are presented to avoid skewing, which can occur with high numeric outliers (mean and median data are presented in tables).

IUs Dispensed. The median monthly factor IUs dispensed for all patients ranged from 29,776 IU to 34,940 IU for the SHL product and from 16,340 IU to 20,912 IU for the EHL product (Appendix A, available in online article). Median monthly IUs dispensed for all patients over the study period were lower in the EHL cohort by 2,142 IU (11% reduction; Figure 1; Table 1), ranging from 32% to 47% reduction compared with SHL users (median monthly use difference, 9,838 IU to 16,514 IU; Appendix A). This was true for patients on prophylaxis (10,530 IU lower) but not for those on episodic on-demand treatment (1,914 IU higher).

Expenditures. The median factor expenditures PPM over the study period were \$23,005 higher (94% increase) in the EHL product cohort (\$47,419) compared with the SHL product cohort (\$24,414; Figure 1; Table 1). This was true both for patients on prophylaxis (\$12,566 higher) and those on episodic on-demand treatment (\$24,751). The median monthly expenditures for all patients ranged from \$38,709 to \$45,422 for the SHL product and from \$46,569 to \$59,599 for the EHL product (Appendix A). Individual median monthly differences for all patients in expenditures ranged from \$6,562 (15% difference between the SHL and EHL products) to a high of \$19,624 (49% difference between the SHL and EHL products) per month.

Mean monthly expenditures for all patients on rFIX replacement products over the study period were 54% higher (\$20,780) in the EHL cohort (\$59,003±\$41,598) than in the SHL cohort (\$38,223±\$45,841; Figure 1; Table 1). The highest mean monthly EHL product expenditure for all patients was \$82,506, while the lowest was \$55,750. The highest mean monthly expenditure for the SHL product was \$61,128, while the lowest was \$48,026 (Appendix A).

The differences in factor IUs (smaller) and expenditures (larger) when these were examined over the entire period compared with the individual monthly expenditures and factor IU differences indicate variations in administrative payment dates, which may be out of strict month synchronization for factor IU delivery and actual payment.

FIGURE 2 Median IUs Dispensed and Expenditures Associated with Switching from a Standard Half-Life (Nonacog Alfa) to an Extended Half-Life (Eftrenonacog Alfa) Recombinant Factor IX Replacement Product, by 3-Month Intervals Before and After Switch^a

Notes: Expenditures are based on 2015 dollars. Box = 25th and 75th percentiles; crossbar = median; whiskers = minimum and maximum values.

^aTruven database.

IUs = international units.

Analysis of the Truven Database (Switch from the SHL to EHL rFIX Replacement Product; Patient-Level View)

Overall, 14 patients who switched from the SHL product to the EHL product were identified from the Truven database. Mean (standard deviation) age in the immediate before and after switch periods was 21.5 (17.3) years (range, 3-64 years). The majority of patients were from the South (50%), followed by the Northeast and West (21.4% each) and North Central (7.1%) areas of the United States.

IUs Dispensed. IUs dispensed were more variable than expenditures, with lower IUs dispensed for the EHL product compared with the SHL product in some 3-month intervals, and greater IUs dispensed for the EHL product than the SHL product in other intervals (Figure 2; Table 2). This same variability was observed when examining the 1-year period before and after switching from the SHL to the EHL product. Fewer units dispensed in the 1- to 3-month interval before switching may represent a drawdown of the patients' personal supply of product in anticipation of the switch from SHL to EHL products. Patients typically order a 1- to 3-month supply so they have factor available in their homes for regular administration and to treat a bleed, should one occur.

Mean IUs dispensed decreased by 3,004 IU, while median IUs dispensed increased by 4,775 IU (Table 3). Factor IUs dispensed over the 3-month periods for individual patients are summarized in Appendix B (available in online article). A reduction in IUs dispensed was expected with the EHL product, as the number of units required according to dosing

recommendations is less than that of the SHL product for the same duration of treatment.

Expenditures. Both the mean and median expenditures associated with rFIX replacement product were higher after the switch from the SHL to the EHL product compared with expenditures before the switch for each of the corresponding 3-month (quarterly) time periods (Figure 2; Table 2). Higher expenditures were also observed when examining the entire 1-year period before and after switching from the SHL to the EHL product; mean expenditures increased \$131,748 and median expenditures increased \$107,303 (Table 3). Expenditures over the 3-month periods for individual patients are summarized in Appendix B. As expected, clotting factor concentrate expenditures accounted for the majority of total health care expenditures (96%-100%).

Discussion

National health expenditures in the United States grew 5.8% to \$3.2 trillion in 2015, which equates to \$9,900 per person and accounts for 17.8% of the Gross Domestic Product.¹³ Projected health spending is expected to be higher than that of the recent past as a result of the changing health care and economic environment and growth in medical prices. Importantly, prescription drug spending increased to \$328 billion in 2015.

The rise in prescription drug spending from 2010 to 2014 was attributed to the following: 10% increase owing to population growth, 30% increase because of an increase in the number of prescriptions per person, 30% increase attributable

TABLE 2 Patient-Level Analysis of Factor Concentrate IUs Dispensed and Expenditures by 3-Month Intervals Before and After Switch from SHL to EHL Product^a

Parameter	Months Before Switch					Months After Switch			
	10-12 (n = 10)	7-9 (n = 12)	4-6 (n = 13)	1-3 (n =14)		1-3 (n = 14)	4-6 (n = 14)	7-9 (n = 9)	10-12 (n = 7)
IUs dispensed									
Mean	61,724	90,574	106,527	54,839	S	88,226	54,716	57,795	61,667
SD	47,559	63,979	100,472	33,315	W	66,909	39,148	47,022	58,547
Minimum	21,000	23,680	29,080	16,160	I	3,724	2,636	6,477	15,204
Lower quartile (25th percentile)	25,200	42,040	46,760	32,120	T	26,200	23,120	19,548	18,801
Median	42,545	73,660	75,880	43,310	C	74,056	45,647	50,888	43,276
Upper quartile (75th percentile)	105,045	118,900	106,900	78,000	H	116,096	90,930	90,930	90,749
Maximum	153,300	243,030	351,600	118,560		214,768	113,806	140,115	180,110
Expenditures, \$									
Mean	67,797	112,011	134,512	67,143	S	262,949	182,245	183,893	192,555
SD	54,756	87,216	131,186	36,744	W	180,288	106,685	138,207	149,826
Minimum	23,741	29,237	36,337	24,884	I	46,719	37,483	35,244	43,730
Lower quartile (25th percentile)	29,947	43,885	52,461	39,045	T	140,781	83,728	67,613	70,829
Median	51,881	77,523	89,389	55,726	C	205,724	183,451	147,363	173,515
Upper quartile (75th percentile)	56,853	140,741	130,326	94,376	H	352,001	275,194	311,146	242,494
Maximum	178,090	298,841	412,591	132,654		613,494	330,834	383,655	493,181

Notes: Data presented for the SHL product are specifically for nonacog alfa, and data presented for the EHL product are specifically for eftrenonacog alfa. Expenditures are based on 2015 dollars.

^aTruven database.

EHL = extended half-life; IUs = international units; SD = standard deviation; SHL = standard half-life.

to overall economy-wide inflation, and 30% increase owing to changes in drug prescription patterns to higher-priced products or price increases for drugs in excess of inflation rates.¹⁴ Specialty drug products contributed significantly to the rise in prescription drug spending, increasing annually at a rate of approximately 11% from \$14.5 billion in 2009 to \$27.1 billion in 2015.¹⁴ In addition, Medicare Part D established a specialty tier threshold of \$600 out of pocket per individual per month, and drugs that exceeded this price point from 2009 to 2015 had an average 22% share of prescription drug spending that appears to be rising; the specialty tier threshold was recently increased to \$670 in 2017.¹⁴

Hemophilia is a chronic and costly disease.¹⁵ Comprehensive care of patients with hemophilia includes visits with the care team of hematologists, physical therapists, registered nurses, and clinical pharmacists, and use of hospital and/or emergency department facilities.^{15,16} However, these factor replacement product expenditures are a small fraction (10%-15%) of the total health care expenditures.^{4,15,17} In 2002, Rogoff et al. found that replacement factor prices increased 1.7% per year over a 9-year period.¹⁸ When they controlled for increased factor consumption, the main source of the price increase was the use of new products that were priced an average of 68% higher than the product that was replaced.

These findings raise questions about whether the advancement in new products is commensurate with increased expenditures.^{17,19} The hemophilia community recognized the theoretical safety difference between plasma-derived and recombinant products and favored recombinant therapies as standard of care.^{19,20} However, with regard to recombinant products, annualized bleeding rates were similar with a once-weekly prophylactic SHL product (3.6) and an EHL product (3.12) in their respective clinical studies.^{9,11} The EHL product was priced to create parity with existing SHL therapies on an annual therapy expenditures basis, understanding that dispensed factor data were derived from selected clinical trials and proprietary pharmacy surveys.^{21,22} Since the EHL product is dosed with fewer weekly IUs, the price per IU was set higher.¹²

Achievement of pricing parity would necessitate, across all users, a reduction in IU use of approximately 63% following a switch from a twice-weekly regimen using an SHL rFIX product to a once-weekly regimen using an EHL rFIX product²¹; if a weekly dosing strategy is considered, a 50% reduction would be required, as the recommended dosing with an EHL rFIX product is approximately half that of an SHL rFIX product (EHL, 50 IU/kg weekly⁸; SHL, 100 IU/kg weekly⁶). It is notable that 1 of the 2 recommended dosing strategies in the EHL product's labeling (100 IU/kg every 10 days vs. 50 IU/kg/week)⁸ would

TABLE 3 Patient-Level Analysis of Factor Concentrate IUs Dispensed and Expenditures for 1 Year Before and 1 Year After Switching from the SHL to the EHL Product^a

Parameter	IUs Dispensed			Expenditures, \$		
	Before Switch (SHL Use)	After Switch (EHL Use)	Change in IUs After Switch from SHL to EHL	Before Switch (SHL Use)	After Switch (EHL Use)	Increased Expenditures (SHL to EHL Switch)
Mean	80,923	77,919	-3,004	99,718	231,466	131,748
SD	57,052	59,816	2,764	66,534	163,923	97,389
Minimum	32,120	7,910	-24,210	39,045	46,719	7,674
Lower quartile (25th percentile)	39,375	27,978	-11,398	51,157	115,689	64,532
Median	59,623	64,398	4,775	75,861	183,164	107,303
Upper quartile (75th percentile)	101,965	113,144	11,179	127,928	330,650	202,722
Maximum	233,200	214,768	-18,432	266,225	613,494	347,269

Notes: Data presented for the SHL product are specifically for nonacog alfa, and data presented for the EHL product are specifically for eftrenonacog alfa. Expenditures are based on 2015 dollars.

^aTruven database.

EHL=extended half-life; IUs=international units; SD=standard deviation; SHL=standard half-life.

actually result in 40% more monthly use than the other strategy and would incur a commensurate increase in expenditures.²¹

Results of our analysis provide further information about IUs of factor dispensed and about expenditures for these rFIX replacement products. From the population-level view, the national specialty pharmacy database profiled data for a large number of patients over the 15-month study period, documenting lower IUs dispensed (11%) and higher expenditures (94%) for the EHL product compared with the SHL product. Expenditures were uniformly higher with the EHL product use across prophylaxis and episodic (on-demand) regimen patients; in addition, episodic on-demand patients had more EHL than SHL factor IUs dispensed (1,914; 15%), possibly related to guidance in the EHL product's labeling advising a higher target FIX activity in the setting of uncomplicated hemarthrosis.⁸

The numbers of episodic on-demand patients were small, as would be expected, since the majority of EHL product use is in the prophylaxis patient group. Real-world experience with the EHL product is limited, but the median weekly prophylactic dose in the pivotal clinical study was 47.3 IU/kg/week, which translates to 13,244 IU per month for a 70-kg person.²³ The national specialty pharmacy data showed median monthly EHL product IUs dispensed ranging from 16,340 IU to 20,912 IU, suggesting that real-world consumption may be greater than expected.

The Truven database identified a small number of patients who served as their own controls and were followed over time as they switched from the SHL to the EHL product. The examples of greater-than-anticipated IUs dispensed for the EHL product in this component of the analysis—that is, a dispensation that failed to comprise at least a 50% reduction

from the patient's baseline on the SHL product, before the switch—may disrupt the paradigm of pricing parity and drive higher expenditures. Even in cases of a 30% reduction in mean IUs dispensed, for instance, a mean expenditure increase of 54% would result (Figure 1). When comparing the 3-month period after switching from the SHL to the EHL product to the 3-month period before, we found that IUs dispensed and expenditures for the EHL product were consistently higher.

These findings run counter to the expected lower dispensed factor and expenditure parity for the EHL product and may be related to the complex pharmacokinetics of rFIX replacement products and lack of known translation between half-life for the SHL product to that for the EHL product in individual patients.²¹ Transitioning from an SHL to an EHL product may require pharmacokinetic analysis to comprehensively assess each patient's needs, leading to variability in the dosing to achieve optimal outcomes.²¹ For prophylaxis specifically, the increased expenditures observed in this analysis may be in part attributable to higher IUs dispensed than would be expected based on dosing published in the literature in the case of the EHL product, and to lower-than-postulated IUs dispensed for the SHL product.²³ This finding also contrasts with an anticipated reduction in factor use based on eftrenonacog alfa dosing, used to establish its pricing structure.^{12,21}

Limitations

The retrospective nature of this analysis is a limitation but was intended to provide a basis for understanding the current evolving treatments for hemophilia B. The challenges associated with data acquisition in rare diseases are based on their small sample sizes and geographically diverse populations, as well as evidence gaps related to the natural history and course

of the disease.²⁴ Study samples were not randomly assigned, which may have introduced a treatment choice bias.

Because approximately 80% of the patients were <40 years of age and 63% of patients had their disease reported as severe, we cannot opine on the implications for older patients and for those with moderate or mild hemophilia B. The databases provided information for claims payments, not for research; thus, in most cases, variables such as patient weight, disease characteristics, fidelity to treatment regimen, and number of bleeding events (if any) are unknown or were not present in all databases. Additionally, with regard to expenditures, the effects of other, subsequent discounts not already captured in the Truven data (if any) or distribution expenditures are unknown.

Prospective data analyzing SHL and EHL products with a well-characterized patient population (e.g., weight, treatment regimens, and bleeding events) are needed. In addition, it cannot be assumed, based on prescription data, that the prescribed units were infused.

Conclusions

This analysis of real-world data shows that expenditures associated with the use of an EHL rFIX replacement product, including in the prophylaxis setting, were higher than expenditures with the SHL product. Additional studies with larger sample sizes are needed to examine the hypotheses generated from this real-world data analysis.

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DISCLOSURES

This study was sponsored by Pfizer. Pfizer employees were involved in the study design; the collection, analysis, and interpretation of data; the review of the manuscript; and the decision to submit for publication. All authors are employees of Pfizer. No author received an honorarium or other form of payment related to the development of this manuscript.

Data from this paper were presented in part at the European Association for Haemophilia and Allied Disorders Annual Meeting, February 1-3, 2017, Paris, France; at the International Society for Pharmacoeconomics and Outcomes Research Annual Meeting, May 20-24, 2017, Boston, MA; and at the International Society on Thrombosis and Haemostasis Congress, July 8-13, 2017, Berlin, Germany.

ACKNOWLEDGMENTS

The authors thank Bina J. Patel, PharmD, and Michelle McDermott, PharmD, of Peloton Advantage, Parsippany, NJ, for medical writing and editorial support, which was funded by Pfizer.

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Real-World Analysis of Dispensed IUs of Coagulation Factor IX and Resultant Expenditures in Hemophilia B Patients Receiving Standard Half-Life Versus Extended Half-Life Products and Those Switching from Standard Half-Life to Extended Half-Life Products

APPENDIX A Population-Level Analysis of Median and Mean IUs Dispensed and Monthly Expenditures of Recombinant Factor IX Replacement Products^a

Parameter	Apr 2015 (n=114)	May 2015 (n=118)	Jun 2015 (n=12)	Jul 2015 (n=121)	Aug 2015 (n=118)	Sep 2015 (n=129)	Oct 2015 (n=133)	Nov 2015 (n=113)	Dec 2015 (n=130)	Jan 2016 (n=115)	Feb 2016 (n=108)	Mar 2016 (n=128)	Apr 2016 (n=115)	May 2016 (n=120)	Jun 2016 (n=119)
Median and mean IUs dispensed															
EHL cohort, n	32	35	42	37	42	46	50	39	54	48	43	54	46	50	51
Median	17,327	20,912	19,183	17,340	18,924	17,340	17,868	19,512	17,883	18,426	18,426	18,426	16,340	18,354	20,412
IQR	12,522-36,372	10,524-28,767	12,124-38,220	10,070-25,416	12,124-28,122	10,070-28,122	10,070-33,814	10,656-34,680	10,600-32,680	10,628-26,707	8,112-31,146	12,264-36,852	10,220-25,122	11,424-36,708	12,516-36,708
Mean (SD)	28,949 (29,741)	23,861 (18,387)	26,440 (20,288)	19,561 (13,554)	22,963 (17,059)	23,383 (24,379)	26,045 (26,952)	23,674 (18,327)	23,135 (16,718)	21,491 (15,144)	22,210 (16,954)	25,923 (21,921)	21,757 (22,399)	23,997 (17,635)	25,016 (17,295)
SHL cohort, n	83	85	90	85	76	86	84	74	76	67	67	74	69	70	68
Median	30,600	30,750	31,590	30,500	30,300	30,360	32,520	32,271	34,158	34,940	34,080	34,141	29,776	33,660	32,569
IQR	12,800-43,560	14,960-47,250	15,840-50,520	18,700-45,172	15,915-45,522	15,900-48,480	20,070-51,482	17,446-56,352	17,436-49,920	20,800-52,380	21,300-59,220	21,300-55,616	18,438-43,748	20,456-57,950	16,520-65,920
Mean (SD)	36,943 (32,773)	37,382 (30,916)	44,090 (52,473)	40,139 (44,872)	41,102 (47,882)	39,175 (42,357)	46,260 (60,467)	44,755 (49,565)	44,169 (40,634)	42,751 (43,909)	45,614 (48,354)	47,022 (63,642)	38,775 (44,312)	42,892 (44,740)	46,821 (51,390)
Difference in median IUs dispensed (EHL-SHL)	-13,273	-9,838	-12,407	-13,160	-11,376	-13,020	-14,652	-12,759	-16,275	-16,514	-15,654	-15,715	-13,436	-15,306	12,157
% difference in median IUs dispensed (EHL-SHL)	-43	-32	-39	-43	-38	-43	-45	-40	-48	-47	-46	-46	-45	-45	37
Median and mean monthly expenditures, \$															
EHL cohort, n	32	35	42	37	42	46	50	39	54	48	43	54	46	50	51
Median	49,382	59,599	54,672	49,419	53,933	49,419	50,924	55,609	50,967	52,514	52,514	52,514	46,569	52,309	58,174
IQR	35,688-103,660	29,993-81,986	34,553-108,927	28,700-72,436	34,553-80,148	28,700-80,148	28,700-96,370	30,370-98,838	30,210-93,138	30,290-76,114	23,119-88,766	34,952-105,028	29,127-71,598	32,558-104,618	35,671-104,618
Mean (SD)	82,506 (84,763)	68,004 (52,402)	75,354 (57,822)	55,750 (38,629)	65,446 (48,619)	66,640 (69,481)	74,227 (76,815)	67,472 (52,232)	65,935 (47,647)	61,250 (43,160)	63,298 (48,320)	73,881 (62,474)	62,008 (63,837)	68,391 (50,259)	71,295 (49,291)
SHL cohort, n	83	85	90	85	76	86	84	74	76	67	67	74	69	70	68
Median	39,780	39,975	41,067	39,650	39,390	39,468	42,276	41,952	44,405	45,422	44,304	44,383	38,709	43,758	42,339
IQR	16,640-56,628	19,448-61,425	20,592-65,676	24,310-58,724	20,690-59,179	20,670-63,024	26,091-66,926	22,680-73,258	22,667-64,896	27,040-68,094	27,690-76,986	27,690-72,301	23,969-56,872	26,593-75,335	21,476-85,696
Mean (SD)	48,026 (42,604)	48,596 (40,190)	57,317 (68,214)	52,181 (58,333)	53,433 (62,247)	50,927 (55,065)	60,137 (78,607)	58,181 (64,434)	57,420 (52,824)	55,576 (57,081)	59,298 (62,860)	61,128 (82,734)	50,408 (57,606)	55,760 (58,162)	60,867 (66,807)
Difference in median expenditures (EHL-SHL)	9,602	19,624	13,605	9,769	14,543	9,951	8,648	13,657	6,562	7,092	8,210	8,131	7,860	8,551	15,835
% median expenditure difference (EHL-SHL)	24	49	33	25	37	25	20	33	15	16	19	18	20	20	37

Notes: Data presented for the SHL product are specifically for nonacog alfa, and data presented for the EHL product are specifically for eftrenonacog alfa. Expenditures are based on 2015 dollars.

^aNational Specialty Pharmacy Database.

EHL = extended half-life; IQR = interquartile range; IUs = international units; SD = standard deviation; SHL = standard half-life.

Real-World Analysis of Dispensed IUs of Coagulation Factor IX and Resultant Expenditures in Hemophilia B Patients Receiving Standard Half-Life Versus Extended Half-Life Products and Those Switching from Standard Half-Life to Extended Half-Life Products

APPENDIX B Individual Patient IUs Dispensed and Factor Concentrate Expenditures by 3-Month Intervals Before and After Switch from the SHL to EHL Product^a

Patient	SHL Treatment Period (Before Switch to EHL Product)					EHL Treatment Period (After Switch from SHL Product)				All Available Quarters	
	4th Qtr	3rd Qtr	2nd Qtr	1st Qtr		1st Qtr	2nd Qtr	3rd Qtr	4th Qtr	Before Switch	After Switch
Individual patient IUs dispensed											
1	35,300	48,960	48,960	16,160	S W I T C H	59,360	72,080	–	–	37,345	65,720
2	47,840	35,120	29,080	22,058		26,064	13,032	19,548	15,204	33,525	18,462
3	153,300	102,700	101,500	50,360		70,304	35,152	–	–	101,965	52,728
4	25,200	23,680	46,760	71,040		26,200	30,310	12,124	43,276	41,670	27,978
5	21,000	243,030	291,440	45,920		103,964	87,032	112,092	58,578	150,348	90,417
6	–	51,010	76,110	25,870		16,224	–	–	–	50,997	16,224
7	105,045	163,268	75,880	32,480		148,290	113,806	–	–	94,168	131,048
8	–	–	122,160	118,560		98,250	90,930	90,930	90,749	120,360	92,715
9	21,100	34,000	61,700	40,700		77,808	56,142	55,278	–	39,375	63,076
10	46,090	65,920	33,760	35,360		61,612	23,120	50,888	24,952	45,283	40,143
11	–	–	–	32,120		214,768	–	–	–	32,120	214,768
12 ^b	39,000	117,000	39,000	78,000		3,724	2,636	6,477	18,801	68,250	7,910
13	–	–	–	84,322		116,096	110,192	–	–	84,322	113,144
14	–	–	351,600	114,800		212,505	93,390	140,115	180,110	233,200	156,530
Median	39,000	58,465	68,790	43,310		74,056	64,111	53,083	43,276	59,623	64,398
Factor concentrate expenditures, \$											
1	51,880.99	75,392.34	75,392.33	24,884.39	S W I T C H	178,649.81	216,931.90	–	–	56,887.51	197,790.86
2	56,852.94	43,884.97	36,336.85	27,562.53		75,072.86	37,482.88	56,224.32	43,730.04	41,159.32	53,127.53
3	178,090.41	119,307.79	123,982.82	61,515.02		203,474.50	103,389.00	–	–	120,724.01	153,431.75
4	29,947.31	29,237.02	57,733.25	87,711.06		68,975.82	88,111.16	35,244.47	125,803.32	51,157.16	79,533.69
5	24,490.20	298,840.60	412,591.48	65,008.90		352,001.19	294,672.88	379,521.00	198,333.32	200,232.80	306,132.10
6	–	69,469.48	103,652.66	35,231.82		46,719.24	–	–	–	69,451.32	46,719.24
7	142,703.62	221,799.52	103,082.94	44,124.06		431,078.87	330,833.94	–	–	127,927.54	380,956.41
8	–	–	136,669.66	132,654.22		262,297.75	242,771.00	242,771.00	242,494.34	134,661.94	247,583.52
9	23,741.14	41,783.61	75,695.17	49,936.17		207,972.97	149,970.50	147,665.75	–	47,789.02	168,536.41
10	55,692.83	79,654.41	40,793.88	42,727.25		178,052.44	66,814.44	147,061.19	70,828.75	54,717.09	115,689.21
11	–	–	–	39,044.84		613,494.27	–	–	–	39,044.84	613,494.27
12 ^b	46,776.34	140,740.68	47,188.00	94,376.00		140,780.54	79,345.06	79,001.97	173,515.40	82,270.26	118,160.74
13	–	–	–	103,798.48		340,398.57	320,901.11	–	–	103,798.48	330,649.84
14	–	–	401,019.39	131,431.13		582,313.29	255,715.01	383,654.64	493,180.88	266,225.26	428,715.96
Median	51,880.99	77,523.38	89,389.06	55,725.60		205,723.74	183,451.20	147,363.47	173,515.40	75,860.79	183,163.63

Notes: Data presented for the SHL product are specifically for nonacog alfa and data presented for the EHL product are specifically for eftrenonacog alfa. Expenditures are based on 2015 dollars.

^aTruven database.

^bPatient 12 manifested low units dispensed but high expenditures, which may represent nonalignment between unit dispensation and actual posting of payments.

EHL = extended half-life; IUs = international units; Qtr = quarter; SHL = standard half-life.