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Assessing the Value Proposition of NUWIQ® (Antihemophilic Factor Recombinant): An Illustrative Model in Cost Avoidance

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Assessing the Value Proposition of NUWIQ® in the Hemophilia A Market: An Illustrative Model in Cost Avoidance

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EXECUTIVE SUMMARY

With the many advances and introduction of new therapies for treating people with hemophilia A, this paper posits an illustrative model for assessing the value proposition of selected factor VIII (FVIII) replacement concentrates. Five marketed recombinant FVIII (rFVIII) products are compared across 4 major areas of hemophilia management: prophylaxis (preventive treatment), breakthrough bleed resolution, on-demand treatment, and inhibitor management. The 5-product landscape is set in a hypothetical health plan with 525 hemophilia A patients. Analysis inputs included are product dose, dosing frequencies, average bleed rates, product price, and high-titer inhibitor development rates. After comparing and contrasting the 5 selected rFVIII replacement concentrates across the 4 major areas, we concluded that cost-avoidance modeling in hemophilia A is worthwhile, possible, and particularly helpful in assessing the value proposition of rFVIII therapies. In our evaluation, we observed that NUWIQ® is a cost-effective rFVIII therapy for treating hemophilia A patients.

With an incidence rate of 1 in 5000 male births annually, hemophilia A is a rare inherited bleeding disorder characterized by a lack or decrease of clotting factor VIII (FVIII).[1] In the United States, there are approximately 20,000 males living with this condition.[1] The severity of hemophilia A is classified by the level of endogenous FVIII as: mild (>5% to 40%), a form that accounts for approximately 25% of cases; moderate (1% to 5%), which accounts for approximately 15% of cases; and severe (<1%), which accounts for approximately 60% of cases.[2] Patients with severe disease are at high risk for bleeding episodes if left untreated.[2]

People with severe hemophilia A can be treated prophylactically to reduce bleeding episodes or on-demand when a bleeding episode occurs. Prophylactic therapy with FVIII is the standard of care for severe hemophilia A, resulting in decreased bleeding episodes and improved quality of life (QOL).

According to a study published in the *Journal of Medical Economics*, the costs of hemophilia increase as the severity of disease increases, with an estimated cost of $301,922 per patient with severe disease on prophylaxis.[3,4] **Figure 1** shows the total annual medical and indirect costs for treating hemophilia A patients at different levels of disease severity.[3]

Clearly, patients with mild or moderate disease require less FVIII replacement than patients with severe disease. However, while experiencing fewer bleeding episodes and emergency room (ER) visits, patients with severe hemophilia A on prophylaxis use more replacement factor than any other group. Additionally, 94% of total medical and indirect costs are attributed to factor utilization for this patient group, as compared to only 54% of the total costs with mild hemophilia A patients. Expectedly, costs vary depending on dosing regimen and product used.

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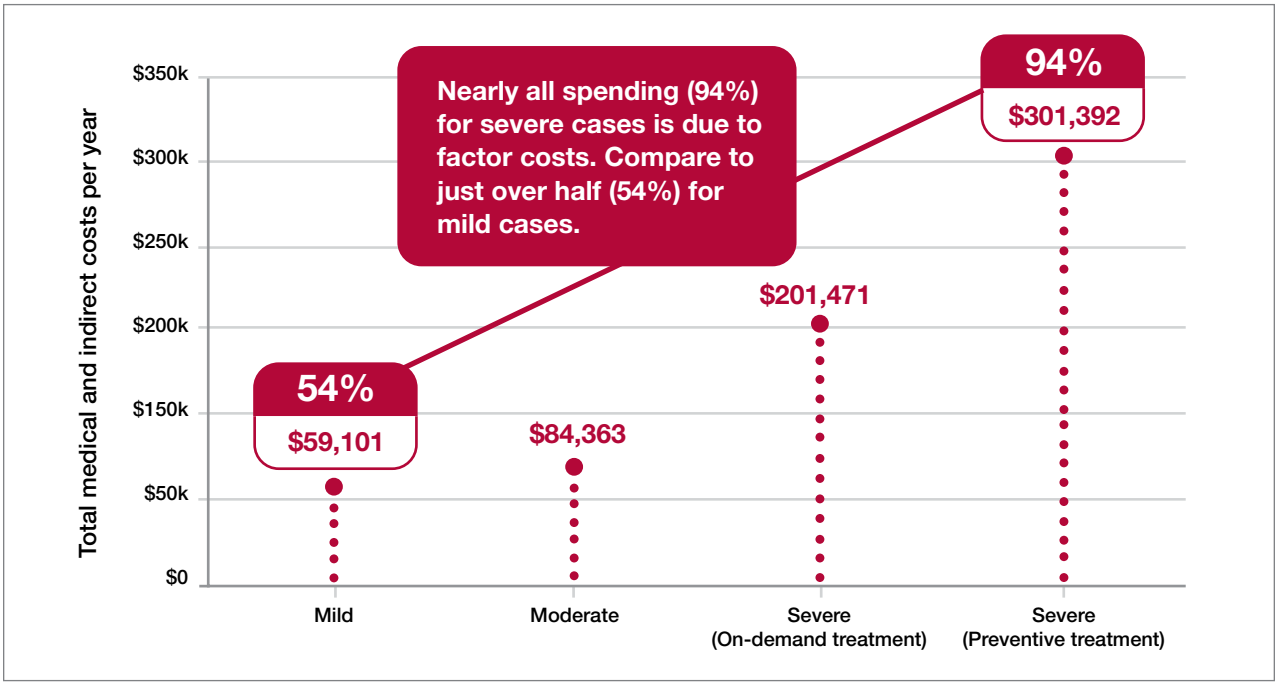

Figure 1. Cost of hemophilia treatment obtained from literature. (Adapted from Optum Inc. *Hemophilia Insight Report.* www.optum.com/content/dam/optum/resources/brochures/Rx/m53018_n_hemophilia_insight_report_0424a.pdf. Accessed August 20, 2020. Data from Zhou ZY, Koerper MA, Johnson KA, et al. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. *J Med Econ*. 2015;18:457-465.)

These costs are greatly increased in patients who develop inhibitors (neutralizing antibodies), which render FVIII replacement therapy less effective in preventing bleeds and increase the risk of uncontrollable bleeding and the development of joint disease.[5] Typically, inhibitors develop in previously untreated patients (PUPs) within the first 20 to 50 exposure days of FVIII therapy and affect approximately 30% of PUPs.[5] Inhibitors are typically managed in 2 ways: management via bypassing agents or treatment via immune tolerance induction (ITI). Bypassing agents like emicizumab circumvent, but do not eradicate, the inhibitors, whereas ITI can eradicate the inhibitors in approximately 70% of cases. While both modalities are expensive, one could argue that the latter option might eliminate the inhibitor in the majority of cases. Therefore, due to increased dose and/or cost of therapy, the cost of managing people with inhibitors can quadruple, as compared to routine prophylaxis (**Figure 2**).

Treatment costs for a person with an inhibitor can exceed $1 million per annum.[3] In the recent Hemophilia Utilization Group Study, adult patients with an inhibitor with employer-sponsored insurance were more likely to use clotting-factor concentrates, more likely to visit the ER, and more likely to require inpatient services than patients without an inhibitor.[6] Despite the relatively high cost of treatment per patient, the relatively low US prevalence rates of hemophilia A compared with other disease states, coupled with physician apathy that hemophilia treatment options lack differentiation, have resulted in a payer environment that does not heavily manage this disease state. This paper seeks to differentiate the various recombinant FVIII (rFVIII) treatment options in hemophilia A to provide a solid foundation for payers to revisit this category for potential future cost avoidance.

Aims of the Study

The treatment of hemophilia has undergone major advances over the past several decades, from use of whole-blood transfusions to the potential of gene therapy/editing cures. Along the way, advances have been achieved in improving safety, effectiveness, manufacturing, and, more recently, the convenience

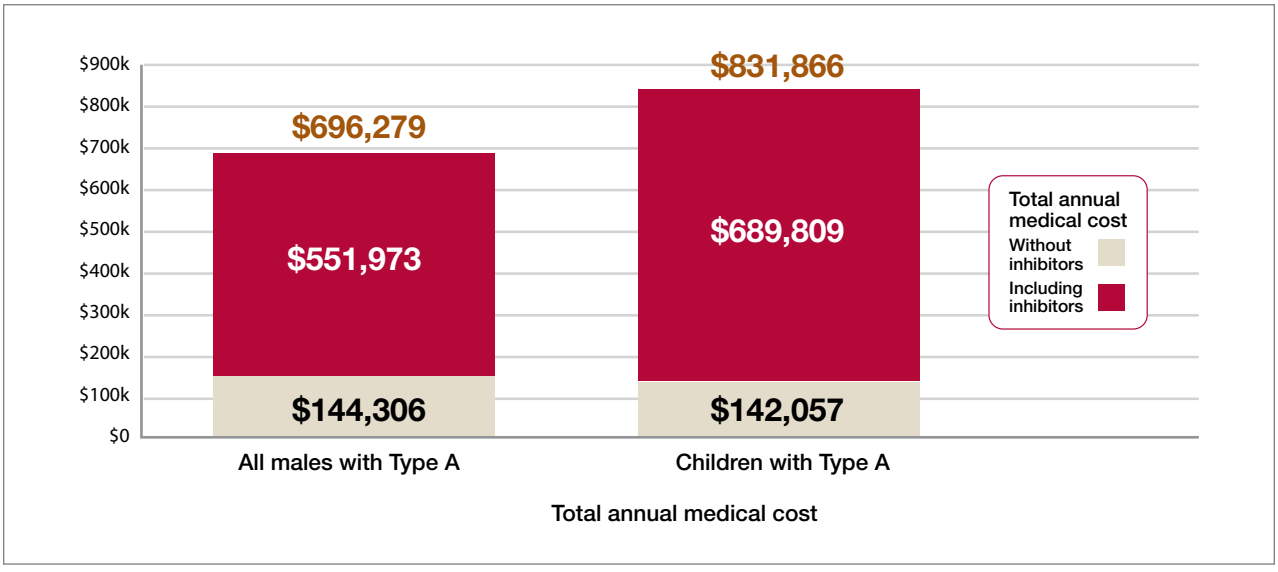

Figure 2. Cost of inhibitor management. (Adapted from Optum Inc. *Hemophilia Insight Report.* www.optum.com/content/dam/optum/resources/brochures/Rx/m53018_n_hemophilia_insight_report_0424a.pdf. Accessed May 8, 2020. Data from Guh S, Grosse SD, McAlister S, et al. Healthcare expenditures for males with haemophilia and employer-sponsored insurance in the United States, 2008. *Haemophilia.* 2012;18:268-275.)

of factor products. The purpose of this study was to examine selected rFVIII replacement products in a hypothetical health plan population by reviewing product use during *prophylaxis*, *breakthrough bleed resolution*, *on-demand treatment*, and *inhibitor eradication*. With the general payer perception that hemophilia A costs are not sizeable enough to warrant active cost-containment efforts, or that there is little-to-no differentiation between the current rFVIII products, this paper seeks to answer fundamental questions such as:

- *Is managing hemophilia A cost required, possible, and worthwhile?*
- *Do all rFVIII products essentially present the same value proposition?*
- *Does treatment with fewer infusions offer cost savings?*
- *Is price the only important contributor to cost avoidance, or is there a more comprehensive approach to understanding the value proposition of various options in the management of hemophilia A?*

Methodology

The cost of managing hemophilia A is generally attributed to costs incurred in 4 key areas: *prophylaxis* (*preventive treatment*), *breakthrough bleed resolution*, *on-demand treatment*, and *inhibitor eradication*. Accordingly, the aim of the study was to make objective comparisons traversing representative antihemophilic factors across these key therapeutic parameters. From a cost-effectiveness perspective, rFVIII products can be categorized based on 2 fundamental types (**Table 1**); each category represents a *distinct value proposition* based on whether it is a *hamster-* versus a *human-cell-line–derived product*. Comparisons were made between 5 newer-generation rFVIII products.[7] For the sake of simplicity, and because the addition of more products would not contribute further to insights, this is intended to be an illustrative model.

The goal was to make objective "apples-to-apples" assessments of value propositions of existing antihemophilic products. It should be noted that the definition of value proposition does not equate simply to low cost, but rather the *clinical value provided*, which is also cost-effective. With this definition in mind, the selection of products in this illustrative model was based on the following criteria:

1. All products selected for the model represent newer-generation rFVIII products. Accordingly, we excluded older rFVIII products that are often

positioned by manufacturers to encourage "cannibalistic switching" to their newer-generation products.
2. All selected products are indicated for use in prophylaxis and on-demand settings. Products not indicated in any of the settings would automatically have an unfair cost-advantage due to lack of utilization in that setting and were therefore excluded.
3. All selected products are capable of eradicating inhibitors. Because the clinical goals, duration of therapy, ultimate outcomes, and pricing of the 2 approaches for treating people with inhibitors were so disparate, we felt that a true "apples-to-apples" comparison with bypassing agents would not be fair. Accordingly, Feiba® and NovoSeven® were excluded.

Because Hemlibra®, a newer nonfactor antihemophilic product, is not indicated for on-demand treatment and can only bypass inhibitors, not eradicate them, it was also excluded. Long-term effects of Hemlibra® on outcomes such as joint and bone health are also unknown. The use of Hemlibra® and FVIII ITI in combination is under investigation for the treatment of patients with inhibitors; however, the effect on FVIII dosing and overall costs would be expected to apply equally to all rFVIII products.

We maintained objectivity by taking a *conservative* and *equitable approach* where possible. For instance, the model assumptions included product dosing, dosing frequency, and average bleed rates based on the respective product's prescribing package inserts (PI), and the average selling price (ASP) of each product was obtained from a common source, the Wolters Kluwer Database. Prophylaxis rates were based on reports from the American Thrombosis & Hemostasis Network (ATHN). Outside of PI-related differences, referenceable inputs were equally applied across the 5 pharmacotherapy options. For example, high-titer development rates were based on the current published literature or company-reported data. Specifically, model variables included product price per international unit ($/IU), dosing regimen, and the number of projected breakthrough bleeds by product and the potential number of patients with inhibitors, by product. Model non-variables included average patient weight (kg) by real-world scenarios; the average number of patients on prophylaxis; the average number of patients treated on-demand as well as the number of bleeds per year; and the number of PUPs in calculating the inhibitor eradication data.

Table 1. **Selected Products: A Representation of All Relevant Categories**[7]

Company	Hamster-derived	Human (HEK cell line)-derived
Takeda	Advate (2003), Adynovate (2015)	
Sanofi		Eloctate (2015)
Octapharma		NUWIQ (2016)
Bayer	JIVI (2018)	

Bottom-line metrics analyzed in this illustrative health plan model included annual utilization of product, annual cost of product, annual per-patient costs across prophylaxis treatment, breakthrough bleed resolution, on-demand treatment, and inhibitor eradication. In addition, the overall output metrics for this hypothetical health plan model show the annual total cost to the health plan by product, per-patient cost by product, per-member-per-month (PMPM) costs for each product, and the annualized total health plan costs of managing 525 hemophilia A patients across all 5 products.

Results

The hypothetical health plan model analyzed data for a population of 525 hemophilia A patients equally divided across the 5 products. First, we observed that for a hypothetical plan comprising a typical mix of 525 hemophilia patients, the total cost is just over $250 million annually, even without factoring any opportunity costs or costs associated with traveling, staffing, or staffing time. So, whereas there is a general perception that the costs of hemophilia management are not high enough to warrant any cost-saving efforts, we would submit to the contrary.

In trying to understand where the differentiation lies among various products, we analyzed the contribution of each parameter to overall costs. We immediately noticed that there is a sizeable variability in pricing, particularly between products. The ASP per unit ranged from $1.339/IU (NUWIQ®) to $2.159/IU (Eloctate®). For the sake of equitability, we assumed equal patient share across products; however, patient shares on products

could certainly vary and have an impact on cost savings, either positive or negative.

Contributions of Individual Parameters

In this section, we delve deeper into why costs may differ between products across hemophilia management parameters: *(A) prophylaxis*, *(B) breakthrough bleed resolution*, *(C) on-demand treatment*, and *(D) inhibitor eradication* (**Table 2**).

A. Prophylaxis

As we review the data points under the prophylaxis section, we start with the assumption, cited in the literature, that 50%, or 250, of 500 previously treated patients (PTPs) in the plan are treated prophylactically. Since we divided patient share equally, 50 patients will use each respective rFVIII product. The results show that estimated annual costs range from $29,243,760 to $44,907,200. The average cost of all 5 products for treating hemophilia A patients prophylactically is $33,702,032. The differences in *price per unit*, *dose*, and *dosing frequency* are quite obvious in the prophylaxis setting. Therapy cost with Eloctate® was higher than with any of the other 4 products, at $44,907,200. For Eloctate®, any economic advantages gained due to lower dosing frequency are offset by higher ASP and average dose/kg. On the other hand, Adynovate® does benefit from having a slightly lower ASP and average dose/kg than Eloctate®. While JIVI® has the lowest utilization of the 5 products in the prophylaxis setting, its 50% higher ASP than NUWIQ® places JIVI® in the second lowest annual cost per patient. In the prophylaxis setting, NUWIQ® and Advate® are similar in profile with respect to frequency of dose and ASP, but NUWIQ® presents the lowest annual cost per patient across the 5 products.

B. Breakthrough Bleed Resolution

Dovetailing off the same base of patients being treated prophylactically, let's turn our attention to outputs for projected *breakthrough bleeds* by product. Utilizing the median *annual bleed rates* (ABR) per each product PI, it can be seen that NUWIQ® has the lowest ABR at 0.9, while Adynovate® and JIVI® have the highest reported ABR at 1.9, followed by Eloctate® at 1.6. When you multiply the ABR per product by 50 patients per product (per ATHN, ~50% of patients are on prophylaxis), you obtain the projected number of bleeds per patient population. NUWIQ® has the lowest projected number of breakthrough bleeds at 45, while Adynovate® and JIVI® have the highest projected number, with 95 annual bleeds each. Utilizing 30 IU/kg as the average dose, which is the upper prescribing PI limit for treating moderate bleeds, and the average patient weight of 80 kg and 1.5 infusions per bleeding episode for breakthrough bleed resolution (same as on-demand), NUWIQ® exhibits the lowest product utilization (216,000 IU) and costs ($289,224), while Adynovate® and JIVI® have the highest product utilization (456,000 IU) and costs ($851,808 and $920,208, respectively). The low ABR with NUWIQ® results in fewer breakthrough bleeds, which significantly lowers costs compared with all competitors in this section. It should be pointed out that, while factor utilization under this parameter is relatively low, the *burden* (to clinicians and patients) and *opportunity cost* of treating a bleed is quite high. We have not factored in additional costs of treating a bleed, such as nurse time, time away from work for the patient, long-term impact on bone health, and impact on QOL.

C. On-demand Treatment

With respect to the on-demand treatment section, the model utilizes the other 50% of the PTPs on the plan, or the residual 250 patients, equally distributed across the 5 products. It is estimated in the literature that each patient assigned to on-demand treatment would experience approximately 40 bleeds per year. Using the prescribing PI for assigning the upper limit of IU/kg dose for each product for treating moderate bleeds in an on-demand treatment setting, and assuming 1.5 infusions per bleeding episode needed to treat, we observed similar utilization rates for all products. Hence the difference in costs within this setting is purely attributed to ASP per unit. Not surprisingly, Eloctate®, JIVI®, and Adynovate® are the 3 most expensive products in this setting, and NUWIQ® and Advate® are almost equivalent, with NUWIQ® being again the most cost-effective.

D. Inhibitor Development Rates and Eradication

As stated previously, about 30% of PUPs with hemophilia A will develop an inhibitor. This statistic has been cited by the US Food and Drug Administration (FDA) and Medical and Scientific Advisory Council (MASAC) guidelines. Peyvandi and colleagues' findings from the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET)

Table 2. **Cost Avoidance Model for a Hypothetical Health Plan**

Hemophilia patients and price	**n = 525**				
Type of cell line	***Hamster***			***HEK***	
Product	**Advate®**	**Adynovate®**	**JIVI®**	**NUWIQ®**	**Eloctate®**
No. of PTPs	**100**	**100**	**100**	**100**	**100**
No. of PUPs	**5**	**5**	**5**	**5**	**5**
Average selling price (ASP)/IU	**$1.374**	**$1.868**	**$2.018**	**$1.339**	**$2.159**
Prophylaxis					
Average no. of patients on prophylaxis	50	50	50	50	50
Average prophylaxis dose/kg	35	45	35	35	50
Average patient weight (kg)	80	80	80	80	80
Annualized frequency of dose	156	104	104	156	104
Annual utilization of product (IU)	21,840,000	18,720,000	14,560,000	21,840,000	20,800,000
Annual cost of product in prophylaxis for all patients in plan by product	**$30,008,160**	**$34,968,960**	**$29,382,080**	**$29,243,760**	**$44,907,200**
Annual cost of product per patient (prophylaxis)	$600,163	$699,379	$587,642	$584,875	$898,144
Breakthrough Bleed (BTB) Resolution					
Bleed rate median ABR; all bleeds for patients on prophylaxis	1.0	1.9	1.9	0.9	1.6
Projected bleeds for all patients in plan by product	50	95	95	45	80
Average dose/kg for treating a BTB	30	30	30	30	30
No. of days of treatment	2	2	2	2	2
Average patient weight (kg)	80	80	80	80	80
Annual utilization of product	240,000	456,000	456,000	216,000	384,000
Annual cost for managing bleeds for all patients in plan by product	**$329,760**	**$851,808**	**$920,208**	**$289,224**	**$829,056**
Annual cost of product per patient (BTB)	$6595	$8966	$9686	$6427	$10,363
On-demand Treatment					
No. of patients on demand	50	50	50	50	50
Average no. of bleeds per year	40	40	40	40	40
Average dose/kg for treating a bleed	30	30	30	30	30
Approximate no. of infusions required to resolve bleeding	1.5	1.5	1.5	1.5	1.5
Average patient weight (kg)	80	80	80	80	80
Annual utilization of product	7,200,000	7,200,000	7,200,000	7,200,000	7,200,000
Annual cost for managing bleeds for all patients in plan by product	**$9,892,800**	**$13,449,600**	**$14,529,600**	**$9,640,800**	**$15,544,800**
Annual cost of product per patient (on-demand)	$247,320	$336,240	$363,240	$241,020	$388,620
Inhibitor Development and Eradication					
High-titer inhibitor development rate (cumulative incidence)	28.40%	28.40%	28.40%	17.60%	15.6%
Potential no. of patients with inhibitors	1.4	1.4	1.4	0.9	0.8
Average dose/kg	200	200	200	200	200
Average patient weight (kg)	25	25	25	25	25
Dosing frequency (days)	365	365	365	365	365
Annual ITI utilization of product for all patients on a product	2,591,500	2,591,500	2,591,500	1,606,000	1,423,500
Annual ITI cost for all patients in plan by product	**$3,560,721**	**$4,840,922**	**$5,229,647**	**$2,150,434**	**$3,073,337**
Annual cost of product per patient (ITI)	$2,507,550	$3,409,100	$3,682,850	$2,443,675	$3,940,175

Table 2. **Cost Avoidance Model for a Hypothetical Health Plan** (continued)

	Hamster			*HEK*	
	Advate®	**Adynovate®**	**JIVI®**	**NUWIQ®**	**Eloctate®**
Result					
Annual total cost to plan by product	**$43,791,441**	**$54,111,290**	**$50,061,535**	**$41,324,218**	**$64,354,393**
Annual total per patient cost by product	**$437,914**	**$541,113**	**$500,615**	**$413,242**	**$643,544**
PMPM cost for each product	**$36,493**	**$45,093**	**$41,718**	**$34,437**	**$53,629**
Annual plan cost of managing hemophilia A across all 5 products	**$253,642,877**				
Annualized units (IUs)	31,871,500	28,967,500	24,807,500	30,862,000	29,807,500
Annual savings with NUWIQ® (assuming equal market share)	**$2,467,223**	**12,787,072**	**8,737,317**		**23,030,175**
Annual savings with NUWIQ® (assuming equal market share %)	**5.97%**	**30.94%**	**21.14%**		**55.73%**
5-year savings with NUWIQ® (assuming equal market share)	$12,336,115	$63,935,360	$43,686,585		$115,150,873

trial validate this data point.[8] Inputting the high-titer inhibitor development rate for each product reported in the literature (mainly SIPPET) and published PUP data for each product, a daily dose of 200 IU/kg (based on the Bonn protocol), and a weight of 25 kg, we see the annual utilization ranges from approximately 1.4 million IU to 2.6 million IU. Having a low high-titer inhibitor development rate, at 17.60%, coupled with the low ASP, NUWIQ® provides the lowest annual costs to treat an inhibitor, at $2,150,434.[9] Although Eloctate® is also a human cell line-derived product like NUWIQ®, it proves to be more expensive, despite the recent announcement of the final results of the PUPs A-LONG Study reporting a lower inhibitor development rate than NUWIQ®.[10] Eloctate® has a 60% greater ASP compared to NUWIQ®.

Contributions of All 4 Parameters

Finally, the annual total cost to the health plan for treating all 525 hemophilia A patients across these 4 major areas is $253,642,877, per the model. The average annual cost of therapy of the 5 products was $50,728,575. NUWIQ® and Advate® were well below the 5-product average costs, while Adynovate® and Eloctate® were well above the average costs. The average total per-patient cost per product was $507,286. The average PMPM cost for treating a hemophilia A patient across all 4 major areas of focus was $42,274. While the PMPM cost of therapy was somewhat similar between NUWIQ® and Advate®, NUWIQ® resulted in the lowest PMPM cost for treating a hemophilia A patient across all 4 major areas of focus. In comparison, the cost of therapy with JIVI®, Adynovate®, and Eloctate® was approximately 21%, 31%, and 56% higher than NUWIQ®, respectively. Over time, such cost avoidance would certainly accrue. For example, assuming equal market share across the 5 products, the 5-year savings from selecting NUWIQ® instead of using Eloctate® would be approximately $115 million. In our model, NUWIQ® now has a 40% market share, and Eloctate® utilization reduces to zero market share. Replacing Eloctate® with NUWIQ® equates to more than $23 million in cost avoidance with NUWIQ® on an annual basis. Applying the same concept, the 5-year savings from selecting NUWIQ® instead of Adynovate®, a hamster-derived product, would be approximately $63 million. Replacing Adynovate® with NUWIQ® equates to more than $12 million in cost avoidance with NUWIQ® on an annual basis.

Limitations

Limitations of this illustrative health plan model analysis include only using the product PIs for dosing and utilization; not considering bypassing agents because they cannot eradicate inhibitors; and not considering nonfactor therapies designed to promote hemostasis through mechanisms other than replacing FVIII. Two challenges, we encountered were that inhibitor rates are not always

included in the PI or not supported by robust PUP studies (except NUWIQ® and Eloctate®). Where possible, we utilized inhibitor development rates from robust studies conducted by pharmaceutical companies in collaboration with physicians and scientists. Where robust data were not available, such as with JIVI®, which was studied only in adults, we defaulted to inhibitor rates from the SIPPET trial,[8] a generally accepted norm despite some limitations. Because this is a theoretical model, we also assumed a 100% compliance rate equally across all products. While we account for product utilization, we do not take into account staff time, patient travel time, and other opportunity costs. This is especially relevant in the management of inhibitors, which is complex and much more difficult than regular bleeds. Plans may vary in their mix of prophylaxis, on-demand, and inhibitor patients, but since it is impossible to accommodate every scenario, we relied on ATHN data, which is a hemophilia database comprising a very robust sample (≥12,000 hemophilia patients). Any limitations that may exist are mitigated by maintaining a consistent, conservative, and equitable approach across all products.

Discussion

A key reason for utilizing ASP was to make the discussion relevant for a majority of customers in the hemophilia A market, including health plan and hospital administrators, pharmacy benefit management organizations, and specialty pharmacy administrators. So, it would be worthwhile to examine our results from those perspectives. A few overarching observations are immediately apparent. Even at a high level, it is easy to optically identify the "trouble spots" in the referenced illustrative model by examining costs in the red font, which denote the highest expenditures in various management settings. In the *prophylaxis* setting, Eloctate® is the most expensive. In the *breakthrough bleed setting*, JIVI® represents the highest spend. In the *on-demand section*, Eloctate® is the most expensive product. JIVI® and Adynovate® are the most expensive in the *inhibitor development* and *eradication* section. Overall, NUWIQ® and Advate® represent the best value propositions quantitatively, and, arguably, NUWIQ® represents the highest value proposition when you take into account the challenge of on-demand therapy, inhibitor management, and providing the lowest PMPM cost for treating a hemophilia A patient across all 4 major areas of focus.

From a purely quantitative standpoint, *prophylaxis* and *on-demand* treatment constitute the lion's share of the cost of the 4 major areas of focus, at approximately 71% and 23%, respectively. The fact that a patient could have up to 40 bleeds annually being treated by on-demand therapy demonstrates that on-demand therapy does not provide the coverage required for bleed protection. So regardless of product, our findings make the case for advocating prophylactic treatment over on-demand treatment where possible.

Although breakthrough bleed resolution is not a substantial contributor to *overall* cost, there are noticeable differences in ABRs between products. With respect to breakthrough bleeding events, NUWIQ® has the lowest ABR at 0.9 and a low ASP. The annual per-patient cost of managing breakthrough bleeds for NUWIQ® is $6427, which is substantially lower than Eloctate®, JIVI®, and Adynovate® and slightly lower than Advate®. While the costs associated with the overall management of breakthrough bleeds are relatively low compared with prophylaxis or on-demand treatment of hemophilia A, the value proposition that NUWIQ® brings in cost and utilization avoidance, as well as other indirect associated reduced resource expenditures for managing breakthrough bleed occurrences, is notable.

As we dig deeper into the less apparent observations of these results, interesting findings on effective management of hemophilia A patients are uncovered. Our first example lies in the *prophylaxis* results section from **Table 2**. The dosing frequencies of Eloctate®, JIVI®, and Adynovate® in this model were 50% lower than those of Advate® and NUWIQ®. Although the dosing frequency should theoretically lower costs, savings are not realized in the case of Eloctate® or Adynovate® because of premium pricing and higher average prophylaxis dose. There is an assumption that the dosing is likely higher to allow for fewer infusions. These hypothetical health plan results are consistent with a real-world evidence study published by Croteau et al in 2019.[11] The purpose of the study was to characterize the longitudinal use of Eloctate®, Adynovate®, and JIVI® compared with other rFVIII product concentrates at 138 hemophilia treatment centers using the ATHN dataset. In their study, the investigators noted that there was no difference in utilization levels between Eloctate®, Adynovate®, and JIVI® compared with other products. Therefore, we might have actually

underestimated Eloctate® and Adynovate® utilization and cost. Croteau et al concluded that it was imperative to pay careful attention to the annual cost of prophylaxis, as the decrease in median prophylaxis consumption was not offset by the higher unit price of these products.[11]

Similarly, our analysis confirms Croteau et al's conclusion that the value proposition of products with a lower recommended dosing frequency is a moot point, because, in effect, any *theoretical* savings assumed due to fewer infusions is offset by their premium price, higher dose/kg, and real-life clinical performance. In the prophylactic setting, only JIVI® showed theoretical cost savings, owing to its lower dose compared to Eloctate® and Adynovate® and fewer number of infusions compared to Advate® and NUWIQ®. Yet, NUWIQ® still proves to be the most cost-effective product in the prophylactic setting. Additionally, in the case of hamster-derived products with a lower recommended dosing frequency, such as Adynovate® and JIVI®, there may be incremental costs above and beyond due to potentially higher inhibitor development rates (based on SIPPET).[8]

According to the National Hemophilia Foundation's MASAC, the most significant current treatment-associated complication of hemophilia A is the development of neutralizing antibodies to FVIII inhibitors. In our health plan model, NUWIQ® is reported to have the lowest high-titer inhibitor development rate among the 5 products. As we have shown, eradicating an inhibitor is extremely expensive. However, NUWIQ® was the least expensive compared to the other 4 products. It is speculated that NUWIQ®'s low high-titer inhibitor development rate could be attributed to the fact that it is produced in the HEK cell line, and thus may lead to decreased immunogenicity, compared with other rFVIII concentrates produced in non-human cell lines. Upon close observation, while per-patient utilization for NUWIQ® is similar to Eloctate®, compared to the other 3 products, it is evident that the overall cost varies substantially based on the ASP differential. Additionally, the impact of the significantly higher inhibitor development rates for the hamster-derived products, coupled with higher ASPs than NUWIQ®, suggest there are more cost-effective alternatives. So, this criterion also offers an opportunity to select products judiciously.

As we summarize this section, it is important to recognize that this illustrative model, which focused on 4 major areas of hemophilia A management, is consistent with the cost of therapy cited in the literature. For instance, our annual per-product costs are consistent with Croteau et al's projected annual cost of therapy. If we separate out and look at the inhibitor development sector of treating PUPs, the costs increase from $2.1 million to $5.2 million. This is substantially lower than the cost reported by Earnshaw et al, as they included cost of hospitalization with ITI.[12] NUWIQ®'s overall value proposition can be attributed to high clinical value in each of the hemophilia treatment settings, coupled with a low ASP. Last, recall that, for the sake of equitability and fairness, we assumed equal distribution of patients across all products. If patient share is increased in favor of a more cost-effective product such as NUWIQ®, incremental savings proportional to utilization could be achieved.

Conclusion

We conclude this paper by addressing the original questions we posed as our aims of the study. Based on our findings:

- The cost of managing hemophilia is indeed high enough to warrant attention.
- Through our relatively simple methodology, we suggest that it is possible for plans and hospitals to objectively assess the value proposition of various rFVIII products.
- The assumption that rFVIII products are essentially commodities is one that could prove costly. For instance, we demonstrate that the savings due to fewer infusions does not always translate to overall cost avoidance.
- Clinical performance of products does vary, and in fact, we observe a series of trade-offs in performance, utilization levels, and, hence, costs in various clinical settings. Depending on a plan's patient mix, attention could be paid to clinical performance in certain areas (eg, inhibitor patients, prophylaxis versus on-demand patients).
- Patient share on a given product is an important consideration. More patients on a cost-effective therapy can increase annual cost avoidance further, and the impact would accumulate over time.
- All parameters and trade-offs were considered across products; we submit that NUWIQ® presents a solid value proposition with opportunities for cost avoidance in treating people with hemophilia A.

The hemophilia market is crowded: There are currently 11 rFVIII antihemophilic products in the market. From an economic perspective, all stakeholders would greatly benefit from looking beyond pricing to the *overall value proposition* of existing antihemophilic products. Evaluating these antihemophilic products in a holistic manner that compares and contrasts clinical trade-offs, patient mix, and pricing in context allows for more efficiency and justification in product selection on formularies, as well as unrealized future cost avoidance.

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