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# Less Is More… A Cost-Minimization Analysis of wilate® as an Effective Treatment Option for von Willebrand Disease

*Charles E. Collins, Jr., MS, MBA*

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## EXECUTIVE SUMMARY

This compendium is a review of selected key clinical and pharmacokinetic studies that informs hospital and payer decision-makers alike of the differences between 2 von Willebrand factor (VWF)/factor VIII (FVIII) concentrates in the treatment of von Willebrand disease (VWD). Upon reviewing the selected key clinical studies that focus on treatment for hemorrhages and the perioperative management of bleeding events in patients with VWD during surgeries, it will become evident that there are significant differences in the number of units used between the 2 concentrates. The selected pharmacokinetic studies provide the insights needed to fully understand the true differences between these 2 concentrates. After applying pharmacoeconomic principles to everyday scenarios for VWD patients, regardless of severity type, the disparity in number of units used between these 2 concentrates solidifies the economic story for wilate®. This white paper provides the salient information proving that wilate® is a cost-effective treatment option for VWD.


In 1926, Dr. Erik von Willebrand was the first to describe a novel blood disorder that was quite different from hemophilia.[1] Known as von Willebrand disease (VWD) today, this disorder is the most common inherited bleeding disorder. Although VWD affects males and females equally, it is well established that the disorder disproportionally impacts females due to menstruation and childbirth. VWD is characterized by a deficiency or dysfunction in von Willebrand factor (VWF). VWF plays a vital role in the initiation of blood clots and provides a homeostatic environment with clotting factor VIII (FVIII). The prevalence of VWD is estimated at 1% of the population.[2] VWD is often underdiagnosed or misdiagnosed due to a lack of a definitive laboratory test and variations in diagnostic criteria.[3]

There are 3 main types of VWD. Type 1 is the most common and mildest form of VWD, occurring in up to 75% of diagnosed patients.[2] It is generally described from a quantitative perspective, as patients with type 1 VWD have a decreased level of normally functioning VWF. Type 2 VWD, which occurs in approximately 20% of diagnosed patients, is characterized by a dysfunction in VWF resulting in a qualitative deficiency in VWF activity even though relatively normal VWF levels are observed.[2] Type 2 VWD is further subdivided into 4 types—2A, 2B, 2M, and 2N—depending on the deficiency caused by the mutation of the *VWF* gene. The most severe and rarest form of VWD is type 3. Patients with type 3 VWD have no measurable VWF, which thus

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negatively impacts FVIII homeostasis and results in excessive bleeding. The prevalence of type 3 VWD is estimated at 1 to 3 per million.[4] The National Organization for Rare Disorders estimates that type 3 VWD affects approximately 5% of patients diagnosed with VWD.[1]

## VWD Treatment Options

Typically, the first line of pharmacotherapy for type 1 VWD is desmopressin acetate (DDAVP). Although its mechanism of action is not completely understood, DDAVP is a synthetic form of vasopressin that increases VWF and FVIII plasma levels, which are believed to be released from cellular storage sites.[5] DDAVP is less effective as a therapy for type 2 VWD and is not indicated for type 3 VWD, since adequate and functioning stores of VWF must be available to be released.[6] Even some type 1 VWD patients may not adequately respond to DDAVP or they might have a more severe bleeding phenotype. Treatment should be individualized according to bleeding severity. Plasma-derived concentrates containing both VWF and FVIII are the next logical pharmacotherapy option. The treatment of patients with VWD is aimed at correcting the dual coagulation defects of abnormal platelet adhesion due to low VWF, as well as correspondingly low FVIII levels. Plasma-derived concentrates, which contain both VWF and FVIII, replace the missing or malfunctioning clotting factors in all VWD types.

This paper focuses primarily on the clinical and economic review of 2 VWF/FVIII concentrates used in the treatment of VWD, wilate® and Humate-P®. Although another concentrate, Alphanate®, was first approved in 1978 for hemophilia A, since it is not indicated for on-demand treatment of bleeding events nor for severe type 3 VWD patients undergoing major surgery, it is not included in the wilate® and Humate-P® comparison cohort.

## Indications and Dosage

### *wilate®*

wilate®, approved by the US Food and Drug Administration (FDA) in 2009, is a von Willebrand factor/coagulation factor VIII complex (human) specifically developed for the treatment of spontaneous and trauma-induced bleeding events in patients with severe VWD as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. wilate® is also indicated for the treatment and the prevention of excessive bleeding during and after surgery in VWD patients. wilate® is a plasma-derived VWF/FVIII concentrate. The ratio of VWF:ristocetin cofactor (RCo) to FVIII coagulant activity (FVIII:C) is 1:1. wilate® is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:[7]

| VWF:RCo/vial | FVIII/vial | Diluent |
|---|---|---|
| 500 IU | 500 IU | 5 mL |
| 1000 IU | 1000 IU | 10 mL |

### *Humate-P®*

Humate-P®, FDA approved in 1986, is an antihemophilic factor/von Willebrand factor complex (human) originally indicated for the treatment and prevention of bleeding in adults with hemophilia A. In 1999, the FDA approved Humate-P® for adults and pediatric patients with VWD for the treatment of spontaneous and trauma-induced bleeding events. In 2007, the FDA approved Humate-P® to prevent excessive bleeding during and after surgery in patients with severe VWD and mild or moderate VWD where the use of desmopressin is known or suspected to be inadequate. Humate-P® is a plasma-derived VWF/FVIII concentrate with a ratio of VWF:RCo to FVIII:C of 2.4:1.

Each vial of Humate-P® lyophilized powder contains the labeled amount of VWF:RCo and FVIII activity. Approximate potencies are shown below:[8]

| VWF:RCo/vial | FVIII/vial | Diluent |
|---|---|---|
| 600 IU | 250 IU | 5 mL |
| 1200 IU | 500 IU | 10 mL |
| 2400 IU | 1000 IU | 15 mL |

## A Review of Key Clinical Studies

### *Bleeding Events*

*Berntorp E, Windyga J, The European Wilate Study Group. Treatment and prevention of acute bleedings in von Willebrand disease–efficacy and safety of Wilate®, a new generation von Willebrand factor/factor VIII concentrate. Haemophilia. 2009;15 (1):122-130.*

Four European prospective, open, uncontrolled, nonrandomized, multi-center phase 2 or phase 3 trials were included in the 2009 Berntorp et al published study.[9] Only patients who met the 2 criteria of not sufficiently responding to DDAVP treatment and also being HIV negative were eligible to participate in these trials. For the treatment or prevention of spontaneous or trauma-induced hemorrhages, the general dosing recommendation of 20-50 IU of wilate® per kilogram of body weight was given. Individual clinical situations dictated the actual dose and duration of treatment.

Altogether 44 patients of all VWD types were included in the 4 clinical studies that evaluated the efficacy and safety parameters of wilate®.[9] Of these, 55% (24 of 44) had severe type 3 VWD, and 43% (19 of 44) were prophylactically treated with wilate® for a cumulative period of 3 months or more (range, 3-47 months). Subject to a separate subanalysis, 18% of the patients (8 of 44) were 12 years of age or younger. Some of the patients participated in more than 1 study.

With all types of VWD being treated with wilate®, a total of 1095 spontaneous or posttraumatic bleeding events in patients were reported (**Table 1**); 92% (1002 of 1095) were in type 3 VWD patients, the most severely affected VWD patient group. Joint bleeds were by far the most prevalent bleeding event, representing 56% (562 of 1002) of bleeds in type 3 VWD patients. In type 2 VWD patients, 53% of all bleeds occurred in the gastrointestinal (GI) tract.

Table 1. **Number of Treated Bleeding Events per Bleeding Site and Type of VWD**

| Predominant Site of Bleeding | VWD Type 1 | VWD Type 2 | VWD Type 3 | Total |
|---|---|---|---|---|
| Joints | 1 | 2 | 562 | 565 |
| Epistaxis | 10 | 13 | 71 | 94 |
| Gastrointestinal | 0 | 34 | 111 | 145 |
| Oral | 2 | 1 | 31 | 34 |
| Menorrhagia | 2 | 0 | 60 | 62 |
| Other (muscle, soft tissue) | 14 | 14 | 167 | 195 |
| Total | 29 | 64 | 1002 | 1095 |

Even with 145 reported GI bleeds, requiring increased doses and treatments, the mean dose per treatment day for all 1095 bleeding events was remarkably only 29 IU/kg of body weight, with a mean of 1.93 treatment days required to stop the bleeding. In the majority of bleeding events that required more than 1 infusion, only 1 infusion per treatment day was administered. Eighty-one percent (885 of 1095) of the bleeding events were successfully stopped in 1 or 2 days. It should be noted that to control GI bleeding events in 2 patients, it took 23 treatment days and 28 treatment days, respectively. In VWD patients with severe GI bleeding events, it is not unusual for such prolonged recovery times; these recovery times are also commonly reported for other products.

### *Product Usage: wilate® vs. Humate-P®*

There are no head-to-head clinical trials comparing the efficacy of wilate® versus Humate-P®. However, in their clinical study Berntorp et al referred to a 97-patient retrospective study (Lillicrap et al) of

Table 2. **On-Demand Treatment of Bleeding Events**

| | wilate®[a] | Humate-P®[b] | Difference |
|---|---|---|---|
| Median dose/infusion for treatment of bleedings | 26 IU/kg | 55 IU/kg | 112% |
| Median number of infusions | 1.93 | 2.02 | 4.7% |

[a]n = 1096 bleeding episodes (type 1 = 29; type 2 = 64; type 3 = 1,002)[9]
[b]n = 344 bleeding episodes (type 1 = 32; type 2 = 77; type 3 = 208; unspecified = 27)[10]

on-demand treatment of 344 bleeding events with Humate-P® where a median VWF:RCo dose of 55 IU/kg was reported.[10] *

In the Berntorp et al study, the reported median dose of VWF:RCo for wilate® was 26 IU/kg, with FVIII:C doses similar between wilate® and Humate-P®, 26 IU/kg and 22 IU/kg, respectively. wilate® has a VWF:RCo median dose that is 47% of the Humate-P® VWF:RCo median dose that was reported in these 2 studies. To be more precise, the Humate-P® median dose of VWF:RCo is more than 2.12 times greater than the wilate® VWF:RCo median dose, showing that, for on-demand treatment of hemorrhages specifically, median IU/kg utilization is 112% greater with Humate-P® than with wilate® in these studies. **Table 2** shows wilate® and Humate-P® in terms of the median dose of VWF:RCo as well as the median number of infusions. The median number of wilate® infusions is 4.7% lower than the median number of Humate® infusions in these studies.

It should be noted that in the Berntorp et al study, 92% of the bleeding episodes were in type 3 VWD patients,[9] whereas in the Humate-P® study only 60% of the bleeding episodes were in type 3 VWD patients.[10] Despite the higher percentage of bleeding episodes in type 3 VWD patients, there were fewer units of VWF:Rco used per patient in the wilate® trial than in the Humate-P® study.

With wilate® having a 4.7% lower median number of infusions and a VWF:RCo median dose that is 47% of the Humate-P® VWF:RCo median dose for on-demand treatment, wilate® should be considered from a utilization minimization perspective. Since the costs per unit of these 2 concentrates are comparable, which we will address later, economic considerations start to take hold.

## Surgical Procedures

*Srivastava A, Serban M, Werner S, et al. Efficacy and safety of a VWF/FVIII concentrate (wilate®) in inherited von Willebrand disease patients undergoing surgical procedures. Haemophilia. 2016;23:1-9.*

wilate® in Subjects With Von Willebrand Disease Who Undergo Surgery (WONDERS) was a prospective, open-label multinational phase 3 clinical study documenting 28 individuals who underwent 30 surgical procedures managed with wilate®.[11] The WONDERS clinical trial investigated the clinical efficacy and safety of wilate® in the prevention and treatment of surgical bleeding in patients with inherited VWD under well-defined, stringent protocol-driven and centrally monitored conditions assessed by the surgeon and investigator and adjudicated by an Independent Data Monitoring Committee (IDMC). Up to 41 surgical procedures were originally planned to be examined in this study. After 30 procedures, a single interim analysis was planned with the possibility for early study termination. The prespecified success rate for study termination was indeed reached after 30 procedures in

*In addition, while the Humate-P® prescribing information states the ratio of VWF:RCo to FVIII:C is 2.4:1, an VWF:RCo/FVIII:C ratio of 2.6:1 was reported for Humate-P® in that analysis.

the interim analysis. Patients were monitored from the start of each surgery for 30 days or until discharge, whichever came later.

A bolus intravenous infusion was administered for all doses. For the *in vivo* recovery (IVR) investigation, all patients received a 60 IU/kg dose of wilate® at study start to calculate the recommended dosing for surgeries. The following additional guidelines were used:

**Major surgery.** A VWF:RCo loading dose of 40-60 IU/kg was given within 3 hours of start of procedure to achieve a peak plasma VWF:RCo level of 100%. A maintenance VWF:RCo dose of 20-40 IU/kg or half of the loading dose was given every 12 to 24 hours.

**Minor surgery.** A VWF:RCo loading dose of 30-60 IU /kg was given within 3 hours of start of procedure to achieve a peak plasma VWF:RCo level of 50%. A maintenance VWF:RCo dose of 20-40 IU/kg or half of the loading dose was given every 12 to 24 hours.

Using the results of the baseline IVR and at the investigator's discretion based on the clinical situation, the dosing recommendations were adjusted for each patient. With the aim of not exceeding a recommended maximum level of 250% FVIII:C and maintaining a recommended trough level of at least 50% VWF:RCo for major surgeries and 30% VWF:RCo for minor surgeries, VIII:C and VWF:RCo levels were monitored throughout the treatment period.

Again, at the interim analysis where the prespecified criteria for success were met, this study was terminated early after 28 individual patients underwent 30 surgeries. Twenty-one procedures were performed in patients with VWD type 3 (70.0%), 7 in patients with VWD type 1 (23.3%), and 2 in patients with VWD type 2 (6.7%). Two patients underwent 2 surgeries; 1 patient with VWD type 1 and 1 with VWD type 3. Of the 30 surgical procedures, 21 were major (70%) and 9 were minor (30%). Among the VWD type 3 patients, 17 of the 21 procedures (81%) were major.

Based on objective criteria and as adjudicated by the IDMC, the overall success rate of wilate® treatment was 96.7%. The success rate was 100.0% for minor surgeries (98.75% confidence interval [CI], 0.569-1.000) and 95.2% for major surgeries (98.75% CI, 0.704-1.000). The overall success rate was 100.0% in VWD type 3 (98.75% CI, 0.785-1.000) and type 2 (98.75% CI, 0.079-1.000) patients, and 85.7% in VWD type 1 patients (98.75% CI, 0.328-0.999). Due to an intraoperative hemostatic efficacy rating of moderate by both the surgeon and IDMC, and a postoperative efficacy rating of good and moderate by the investigator and IDMC, respectively, only 1 procedure was considered unsuccessful due to an intraoperative complication.

Patients received wilate® for a mean of 7.7 days (median, 7.0; range, 3-17) and received a mean total cumulative dose of VWF:RCo of 293.1 IU/kg (median, 270.6; range, 66-700) for loading and maintenance infusions. The mean duration for major surgery patients was 9 days (median, 8.0; range, 4-17), and the mean total cumulative dose was 368.9 IU/kg (median, 360; range, 147-700). The mean duration for minor surgery patients was 4.7 days (median, 4.0; range, 3-10), and the mean total cumulative dose was 116.2 IU/kg (median, 127.5; range, 66-163).

In the Srivastava et al study, patients treated with wilate® received a median loading dose of VWF:RCo of 52.1 IU/kg (range, 27-77) per infusion, whereas the Thompson et al study reports a median loading dose of 82.3 IU/kg (range, 32.5-216.8) in patients treated with Humate-P®.[2] For maintenance infusions, the median dose of VWF:RCo in patients treated with wilate® was 28.5 IU/kg (range, 8-63), as reported by Srivastava et al, while in the Thompson et al study with Humate-P®, the median maintenance dose of VWF:RCo reported was 52.8 IU/kg.[2] **Table 3** shows the median loading dose and median maintenance dose between wilate® and Humate-P® for patients undergoing surgery.

In the surgical setting, a number of studies evaluating the efficacy of VWF/FVIII concentrates other

Table 3. **Perioperative Management of Bleeding Events in Patients with VWD**

| | wilate®[a] | Humate-P®[b] | Difference |
|---|---|---|---|
| Median loading dose/infusion for patients undergoing surgery | 52 IU/kg | 82 IU/kg | 57.7% |
| Median maintenance dose/infusion for patients undergoing surgery | 29 IU/kg | 53 IU/kg | 82.7% |
| Median number of infusions | 6 | 7 | 16.7% |

[a]n = 30 surgical events (type 1 = 7; type 2 = 2; type 3 = 21)[11]
[b]n = 42 surgical events (type 1 = 16; type 2 = 9; type 3 = 8; unspecified = 6)[2]

than wilate® have been published. In 1 prospective study, Humate-P® was deemed effective (excellent or good overall efficacy) in 100% of 42 urgent surgical procedures.[2] The overall number of patients with VWD type 3 was much lower in the Thompson et al[2] study, as compared with the Srivastava et al[11] trial (21% vs. 70%), although the proportion of major procedures was comparable (60% vs. 70%). wilate® dosing was lower than dosing reported for Humate-P® in VWD patients undergoing surgery.

To summarize these findings, wilate® and Humate-P® for patients undergoing surgery have been cited in the literature as being effective (excellent or good overall efficacy).[2,11] However, wilate® use, as Table 3 shows, leads to an almost 58% lower median loading dose per infusion and an 82% lower median maintenance dose per infusion in patients undergoing surgery compared with Humate-P®. It should be noted that throughout the postoperative period, plasma levels of FVIII:C, VWF:RCo, and VWF:Ag were monitored. In the Srivastava study, no thromboembolic events occurred and no accumulation of FVIII:C was observed over time with wilate®.

## Pharmacokinetics Comparison

Considering the risk of FVIII accumulation, there are 2 additional areas of consideration for understanding the differential in utilization in these VWF:RCo/FVIII:C complexes; the first is reviewing the half-life of each component in these VWF:RCo/FVIII:C complexes and its effects on multiple dosing, and the second is reviewing the VWF:RCo/FVIII:C complex activity levels needed to maintain hemostasis. **Figure 1** shows FVIII accumulation occurring following repeat dosing with Humate-P®, whereas no FVIII accumulation occurs with wilate®.[7,12] As in the case of wilate® VWF:RCo/FVIII:C complex, the graph on the right shows that the half-life of component 1 (VWF) is similar to that of component 2 (FVIII); parallel trough and peak curves are observed over repeat doses. In contrast, in the case of Humate-P® VWF:RCo/FVIII:C complex, the graph on the left shows that the half-life of component 1 (VWF) is shorter than that of component 2 (FVIII); as repeat dosing occurs to maintain a steady state for component 1, accumulation of component 2 (FVIII) may occur. Specifically, in surgery, when repeat doses are administered over many days, there may be an increased risk of FVIII accumulation when large differences between the VWF half-life and FVIII half-life exist, as shown in Figure 1A. This difference can be explained by the component half-lives as shown in **Table 4**.[8,13]

**Figure 2** depicts the average plasma peak and trough levels in 28 VWD patients undergoing surgery.[12] The 1:1 VWF:RCo/FVIII:C ratio and parallel pharmacokinetic activity is exhibited. Over the multiple wilate® administrations, no FVIII:C accumulations were observed.

While you can review the half-life differences, the real story is the effect of the half-lives on the recommended repeat dosing regimen between wilate® and Humate-P®. The dosing differential has an impact on the total utilization of product, thus impacting total product costs.

The second area of consideration when dis-

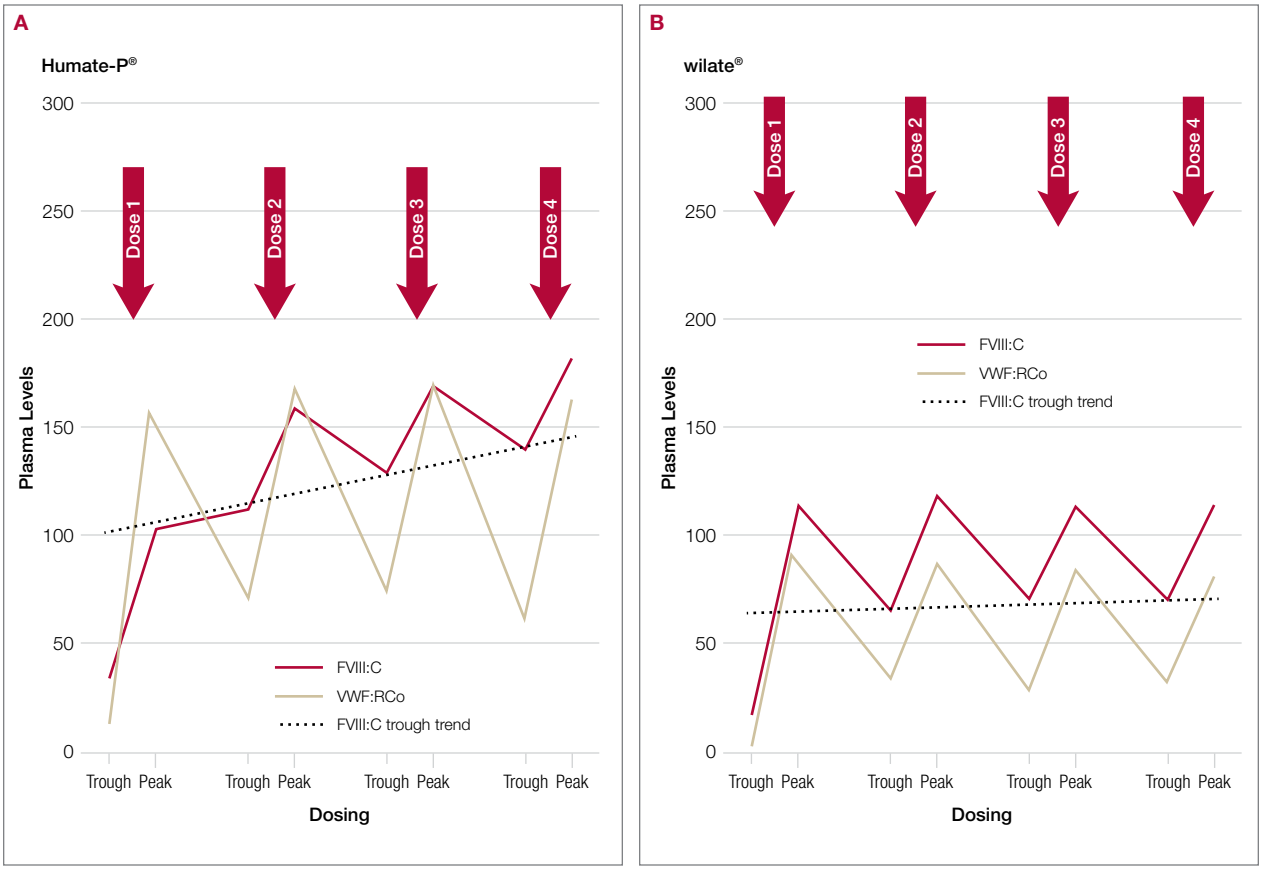


**Figure 1.** Pharmacokinetics of VWF/FVIII complexes during surgery. VWF and FVIII levels were determined 30 minutes before and after each infusion for both complexes. (**A**) With Humate-P®, pre-infusion mean FVIII levels before each maintenance dose progressively increased, in contrast to those of VWF which remained stable.[12] (**B**) With wilate®, both VWF and FVIII plasma levels rise and fall in parallel during maintenance dose administrations.[7]

cussing the differential in utilization in these VWF:RCo/FVIII:C complexes is the activity levels needed to maintain hemostasis. Low levels of VWF activity may result in correspondingly low FVIII activity in patients with VWD. wilate® replaces the missing VWF and FVIII that are needed for effective hemostasis in a physiologic 1:1 ratio. With a 1:1 balanced dosing ratio, wilate® achieves the therapeutic goals for both VWF and FVIII. Therapeutic goals for treatment of bleeding events are defined as:

- > 30% VWF and FVIII trough levels for minor hemorrhages

Table 4. **Component Half-Life of VWF/FVIII Complexes**[8,13]

| Product Name | Terminal Half-life ($t_{1/2}$) of FVIII:C in Any Type (hours) | Terminal Half-life ($t_{1/2}$) of VWF:RCo in Any Type (hours) | Ratio Half-life ($t_{1/2}$) of FVIII:C/VWF:RCo (hours/hours) | Recommended Repeat Dosing (hours) |
|---|---|---|---|---|
| Humate-P® | ~25 | 10-13 | 2.2 | Every (6) 8-12[a] |
| Wilate® | ~20 | ~16 | 1.3 | Every 12-24 |

[a]Patients with shorter VWF and/or FVIII half-lives may require dosing every 6 hours.[8]

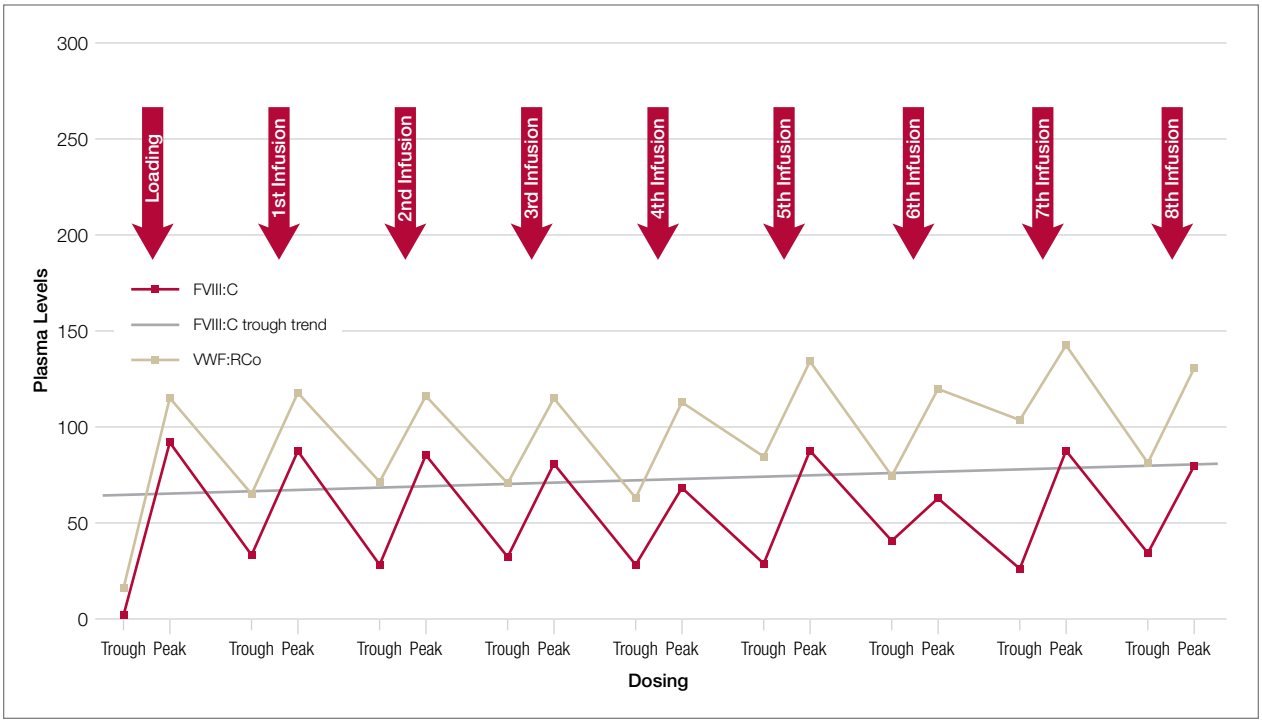


**Figure 2.** wilate® pharmacokinetics during repeat dosing in surgery.[12]

- > 50% VWF and FVIII trough levels for major hemorrhages.

**Figure 3** depicts the mean plasma levels after loading and maintenance doses for both wilate® and Humate-P® for minor hemorrhages in type 2 and 3 VWD patients.[7,14] In this example, to maintain hemostasis for minor hemorrhages, it is quite clear that both the loading dose and maintenance dose of Humate-P® contribute to more utilization when compared to wilate®. If we were to extrapolate this example to apply to major hemorrhages, we can expect a larger unit differential with Humate-P® due to the VWF:RCo to FVIII:C ratio of 2.4:1 when compared to wilate® with a 1:1 balanced dosing ratio.

We have seen that there is a distinct differential in pharmacokinetic profiles between wilate® and Humate-P®, specifically in FVIII kinetics, half-life of the different components, and the levels of activity to maintain hemostasis for minor hemorrhages.[11] All of these factors contribute to the major utilization difference between wilate® and Humate-P®. When we compare the unit cost between wilate® and Humate-P®, given the utilization differences, the real pharmacoeconomic story will unfold.

The literature has noted multiple studies where FVIII:C accumulation has been observed in VWD patients administered Humate-P®, which has a VWF:RCo to FVIII:C ratio of 2.4:1. Due to the parallel pharmacokinetic profiles of VWF:RCo/FVIII:C, wilate® may be beneficial in more accurately estimating dosing and facilitating laboratory monitoring in such surgery scenarios.

## Pharmacoeconomic Comparisons

Now that we have established the unit utilization difference between wilate® and Humate-P® across bleeding events and surgical events, we will now focus on the cost implications by applying the unit cost for each product in typical bleeding and surgical events. According to Wolters Kluwer Medi-Span Price Rx, the unit average selling price (ASP) for wilate® is $1.01/IU and $1.12/IU for Humate-P®.[15]

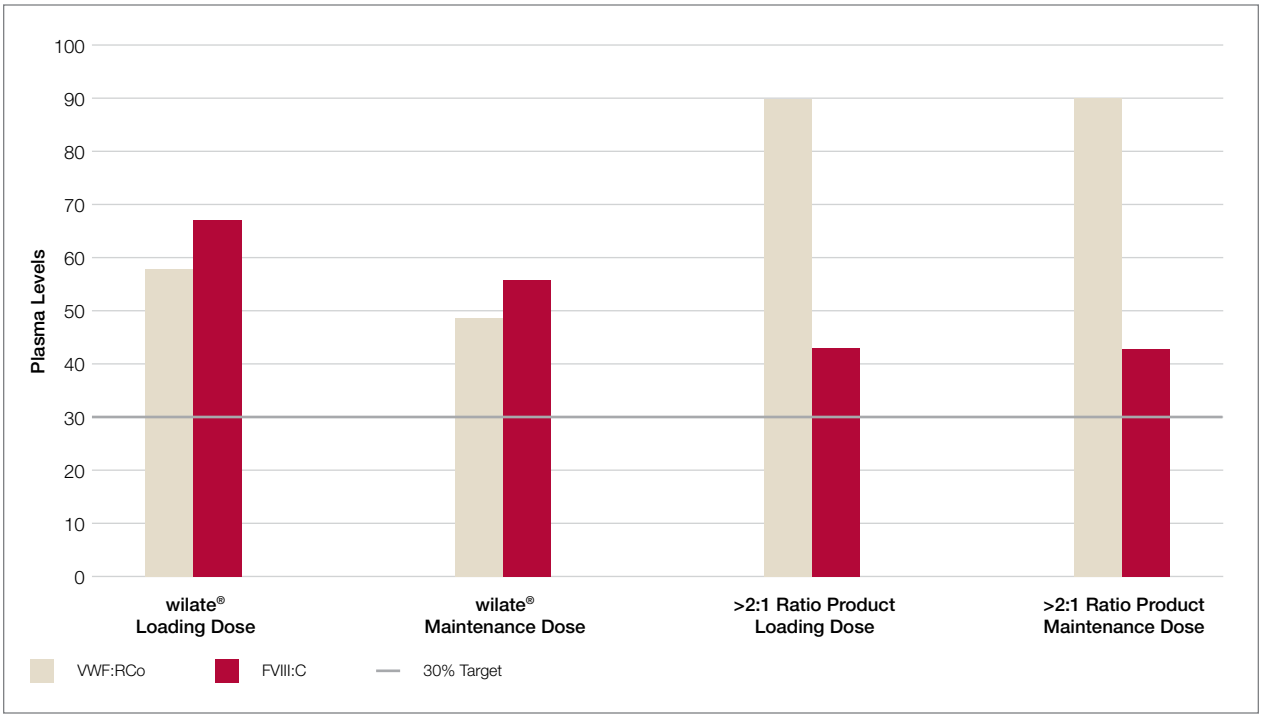


**Figure 3.** Mean plasma levels after loading and maintenance doses for minor hemorrhages in type 2 and type 3 VWD.[7,14]

For both products, all doses in the following scenarios are based on the clinical studies presented in this paper. Results shown are from different clinical trials with differing clinical characteristics and study parameters. Use caution when comparing results from different clinical trials. Lower cost refers only to the cost of product administered and does not refer to any other costs associated with treatment of VWD, such as costs of adverse events, drug administration costs, or hospitalization costs. For consistency purposes, cost comparisons are based on published ASP.

In our first scenario, the product costs for on-demand treatment of hemorrhages (minor and major) across VWD patients (regardless of severity) are reviewed (**Table 5**). These scenarios assume the cost components for treatment of a bleeding episode associated with hemorrhages for a single patient with an average typical weight of 80 kg. As Table 5 demonstrates, wilate® treatment utilizes 4014 IU, or 54.8% fewer units than the 8888 IU of Humate-P® treatment. That translates into a cost avoidance of approximately 59% when you use wilate® over Humate-P® for on-demand treatment of hemorrhages in VWD patients (**Figure 4**).

To put this scenario into perspective, if your hospital system or health plan had just 17 VWD patients/members who needed to be treated for a hemorrhage (minor or major), the hospital system or health plan could avoid $100,810.00 in additional product cost by using wilate® instead of Humate-P®.

In our second scenario, the product costs associated with perioperative management of bleeding for surgeries across VWD patients are reviewed for a single patient with an average typical weight of 80 kg (**Table 6**). As Table 6 demonstrates, Humate-P® utilizes 27,704 IU, or 55% more units than the 17,848 IU of wilate®. That translates into a cost avoidance of approximately 42% when you use wilate® over Humate-P® for perioperative management of bleeding for VWD patients (**Figure 5**).

To put this scenario into perspective, if your hospital system or health plan had just 8 VWD patients/

Table 5. **Product Cost for On-Demand Treatment of Hemorrhages**

| | Humate-P® | wilate® |
|---|---|---|
| Patient weight | 80 kg | 80 kg |
| Dose per infusion (based on median dose reported from key trials) | 55 IU/kg | 26 IU/kg |
| Infusions (based on median number of infusions reported from key trials) | 2 | 2 |
| Total dose (calculated) | 8,888 IU | 4,014 IU |
| Average selling price (reported in Medi-Span Price Rx)[a] | $1.12/IU | $1.01/IU |

[a]Wolters Kluwer Medi-Span Price Rx file accessed on September 19, 2018.

Table 6. **Product Cost for Perioperative Management of Bleeding**

| | Humate-P® | wilate® |
|---|---|---|
| Patient weight | 80 kg | 80 kg |
| Loading dose (based on median loading dose reported in key clinical trials) | 82 IU/kg | 52 IU/kg |
| Maintenance dose (based on median maintenance dose reported in key clinical trials) | 53 IU/kg | 29 IU/kg |
| Infusions (based on median number of infusions reported in key clinical trialsl) | 6 | 7 |
| Total dose (calculated for Humate-P®; based on median total dose reported in wilate® clinical trial) | 27,704 IU | 17,848 IU |
| Average selling price (reported in Medi-Span Price Rx)[a] | $1.12/IU | $1.01/IU |

[a]Wolters Kluwer Medi-Span Price Rx file accessed on September 19, 2018.

members who needed to be treated for perioperative management of bleeding following minor or major surgery, the hospital system or health plan could avoid $104,824.00 in additional product cost by using wilate® instead of Humate-P®.

To summarize the pharmacoeconomic comparison discussion, it has been shown that whether it be an on-demand minor or major hemorrhage or perioperative management of bleeding for a minor or major surgery, wilate® is a less expensive treatment option than Humate-P® from the standpoint of product cost. From a hospital system or health plan perspective, major product cost avoidance may be realized through the use of wilate® versus Humate-P®.

## Summary

The key insights from this white paper have demonstrated a difference between wilate® and Humate-P® for multiple outcomes. In patients who received on-demand treatment of bleeding events in the Berntorp et al clinical study,[9] those treated with wilate® had a 4.7% lower median number of infusions when compared to those treated with Humate-P® in the Lillicrap et al study.[10] In addition, wilate® units consumed were only 47% of Humate-P® utilization.

With respect to surgical procedures, Srivastava et al[11] demonstrated that concentrate utilization is lower with wilate® treatment, with an almost 58% lower median loading dose and an 82% lower median maintenance dose in patients undergoing sur-

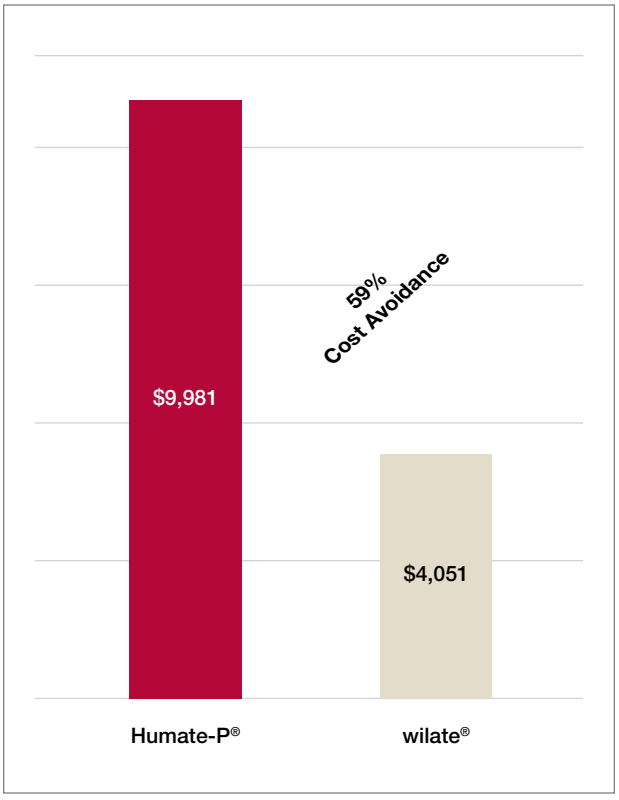


**Figure 4.** Product cost per bleeding event for hemorrhages.

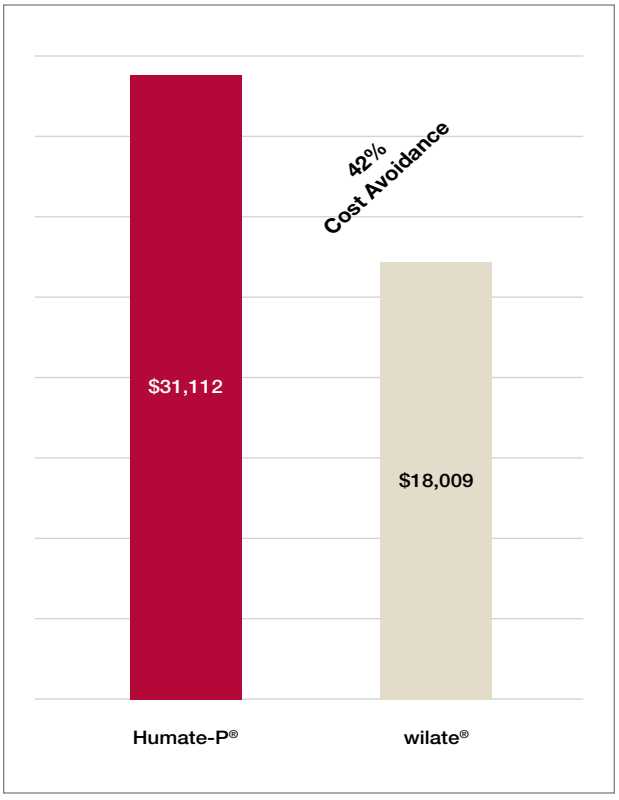


**Figure 5.** Product cost per surgical procedure.

gery, as compared to Humate-P® in the Thompson et al clinical trial.[2] It is also important to note that the Strivastava et al study was terminated early after 28 patients underwent 30 surgeries, as the criteria for success were met at the interim analysis.

We have shown that there are major utilization differences between wilate® and Humate-P®. From a pharmacoeconomic comparison perspective, cost avoidance can be obtained by using wilate® for an on-demand minor or major hemorrhage or perioperative management of bleeding for a minor or major surgery in members with VWD, regardless of severity type.

In conclusion, wilate® should be respectfully considered for formulary inclusion as a cost-effective treatment option for severe VWD when P&T Committees convene.

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