wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

Developed Specifically for the Treatment of Patients with von Willebrand Disease

octapharma

For the safe and optimal use of human proteins

Table of Contents

Octapharma

Octapharma: Committed to advancing human protein therapies

Octapharma is one of the largest plasma product manufacturers in the world, providing a complete range of safe, tolerable, and efficacious human protein therapies. Octapharma was the first manufacturer to apply the solvent/detergent (S/D) process to a large-scale production of FVIII concentrate. With more than 20 years of experience in the development of coagulation products, Octapharma has become a global company with a comprehensive portfolio of human protein therapies.

Octapharma specializes not only in coagulation products for the treatment of bleeding disorders, but also in immunology, transfusion medicine, and intensive care. Currently, patients in over 80 countries around the world are treated with Octapharma products. Additionally, fully integrated production sites in five countries, including two state-of-the-art manufacturing sites licensed by the US Food and Drug Administration (FDA), help to ensure the highest level of production flexibility and sustainable product supply for patients.

Octapharma: Stringent plasma requirements

The safety and quality of plasma products begin with the starting material. wilate® is derived exclusively from large pools of human plasma collected in US FDA-certified plasma donation centers.

Plasma collection centers, donors, and donated plasma are carefully selected and monitored. Octapharma requires all donors to have a US social security number. Every plasma collection center is thoroughly inspected by Octapharma's Quality Assurance auditors and must meet our demanding high standards prior to acceptance. Following initial approval, all plasma centers undergo regular ongoing inspections by both Octapharma and the relevant national authorities.

Every donor undergoes extensive medical examination prior to becoming eligible to donate. All donated plasma undergoes individual unit testing for antibodies against HIV-1/2, HBV, and HCV. In addition, the plasma undergoes PCR (NAT) testing for HIV, HBV, HCV, HAV, and parvovirus B19.

Octapharma has a history of setting the benchmark for product and patient safety by utilizing multiple validated viral inactivation and removal procedures, including solvent/detergent, Pasteurization, Terminal Dry Heat Treatment, and Nanofiltration. As with all plasma-derived products, the risk of transmission of infectious agents cannot be completely eliminated. All product batches undergo rigorous quality control and internal batch release evaluation. In addition, batch release is performed by national and international regulatory agencies, including the FDA.

Please see Important Safety Information on page 9.
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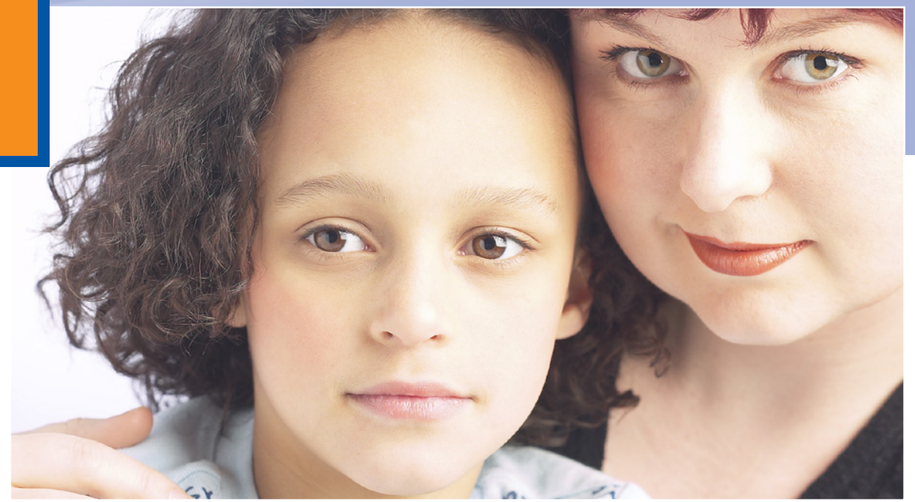

von Willebrand Disease

Presentation and symptoms

von Willebrand disease (VWD) is a commonly encountered inherited bleeding disorder, with type 1 occurring with a prevalence of about 1% in the general population, and clinically relevant cases occurring in about 100 cases/million people (30,000 cases).[1,2] The most common presenting symptom in patients with VWD is bleeding, usually involving mucous membranes and skin sites. Bleeding is usually of mild to moderate severity, reflecting the predominance of type 1 VWD. However, life-threatening bleeding (CNS, gastrointestinal) can occur in patients with type 3 VWD, those with type 2 VWD, and even (rarely) in those with type 1 VWD.[2]

The initial clinical assessment should focus on a personal history of excessive bleeding and family history of bleeding disorders to determine whether the patient may benefit from further diagnostic evaluation.[2]

Initial evaluation and screening questions for bleeding disorders[2]

1. Have you or a blood relative ever needed medical attention for a bleeding problem or been told you have a bleeding disorder or problem:

- During/after surgery?
- With dental procedures, extractions?
- With trauma?
- During childbirth or for heavy menses?
- Ever had bruises with lumps?

2. Do you have or have you ever had:

- Liver or kidney disease; a blood or bone marrow disorder; a high or low platelet count?

3. Do you take aspirin, NSAIDs, clopidogrel, warfarin, heparin?

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Classification of VWD

There are three distinct forms of VWD: type 1, type 2, and type 3. Type 1 involves a partial quantitative deficiency of von Willebrand factor (VWF). Type 2 involves the qualitative VWF defects, including structural or functional defects, of the VWF protein. Type 3 involves a complete deficiency of VWF. In general, the severity of bleeding worsens from type 1 to type 3 disease.[2]

Type	Description[3]	% of patients with VWD[4]
1	Partial quantitative deficiency of VWF	~ 60% - 80%
2	Qualitative VWF defects	~ 10% - 30%
2A	Decreased VWF-dependent platelet adhesion and a selective deficiency of high-molecular-weight multimers	
2B	Increased affinity for platelet glycoprotein Ib	
2m	Decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers	
2N	Markedly decreased binding affinity for Factor VIII	
3	Virtual complete deficiency of VWF	~ 1% - 5%

Diagnosis of VWD

Initial hemostasis laboratory evaluation usually includes a platelet count and complete blood count (CBC), partial thromboplastin time (PTT), prothrombin time (PT), and optionally either a fibrinogen level or a thrombin time (TT). In the past, the activated PTT and bleeding time (BT) were recommended as diagnostic tests. However, many patients with VWD have normal PTT and BT results.[2]

Initial laboratory evaluation of hemostasis[2]

- Complete Blood Count (CBC) and platelet count
- Partial thromboplastin time (PTT)
- Prothrombin time (PT)
- Fibrinogen or thrombin time (TT) (optional)

Initial VWD assays[2]

- VWF:Ag
- VWF:RCo
- VWF:FVIII

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wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

von Willebrand Disease

The VWF protein and its functions

von Willebrand factor (VWF) is a protein made up of identical subunits that form linear strings referred to as multimers. In plasma, factor VIII (FVIII) and VWF bind in a 1:1 ratio, which circulates as a loosely coiled protein complex that does not interact with platelets or endothelial cells under normal conditions. When vascular injury occurs, VWF causes platelet adhesion, activation, and aggregation. This facilitates clotting that is regulated, in part, by FVIII.[2]

Current treatment options for VWD

Treatment of VWD is focused on increasing the availability of VWF and FVIII to correct platelet function through adhesion, aggregation, and hemostatic plug formation. The National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend three approaches for managing VWD:[2]

Adjunctive therapy: Agents, such as antifibrinolytics, topical agents, and oral contraceptives, act to promote hemostasis without altering the VWF concentration.

Non-replacement therapy: Non-replacement therapies, such as Desmopressin: 1-desamino-8-D-arginine vasopressin (DDAVP), enable the release of endogenous VWF by stimulating the endothelial cell with desmopressin, a synthetic derivate of the anti-diuretic hormone vasopressin.

Replacement therapy: Replacement therapies such as wilate® replace the missing VWF by delivering safe concentrates of human plasma-derived, viral-inactivated VWF/FVIII in patients for whom it is indicated (see page 7).

VWF terms and definitions[2]

Designation	Property
von Willebrand Factor (VWF)	Multimeric glycoprotein that promotes platelet adhesion and aggregation and is a carrier for FVIII in plasma
von Willebrand Factor ristocetin cofactor activity (VWF:RCo)	Binding activity of VWF that causes binding of VWF to platelets in the presence of ristocetin with consequent agglutination
von Willebrand Factor antigen (VWF:Ag)	VWF protein as measured by protein assays; does not imply functional ability
von Willebrand Factor collagen-binding activity (VWF:CB)	Ability of VWF to bind to collagen
von Willebrand Factor multimers	Size distribution of VWF multimers as assessed by agarose gel electrophoresis
Factor VIII (FVIII)	Circulating coagulation protein that is protected from clearance by binding to VWF and is important in thrombin generation
Ristocetin-induced Platelet Aggregation (RIPA)	Test that measures the ability of a person's VWF to bind to platelets in the presence of various concentrations of ristocetin

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wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

wilate®: Product Profile

wilate® at a glance

- **High purity VWF/FVIII complex**
- **Double virus inactivated**
- **Physiologic 1:1 ratio of VWF and FVIII**
- **Parallel pharmacokinetic profiles for FVIII and VWF**
- **Clinical efficacy, safety, and tolerability proven in adult and pediatric populations**
- **Rapidly dissolved in a small volume**
- **Convenient dosing interval**

wilate®: Developed specifically for the treatment of patients with von Willebrand disease

Indications: In December 2009, the US FDA granted approval for wilate® for the treatment of spontaneous and trauma-induced bleeding episodes 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.[5]

Clinical trials to evaluate the safety and efficacy of prophylactic dosing with wilate® to prevent spontaneous bleeding have not been conducted in VWD subjects. wilate® is not indicated for the prevention of excessive bleeding during and after surgery in patients with VWD. wilate® is not indicated for Hemophilia A.

Double Virus Inactivation: wilate® is a double virus inactivated VWF/FVIII, high-purity concentrate, utilizing the solvent/detergent (S/D) process (0.3% TNBP, 1.0% Octoxynol-9) and a special terminal dry-heating (TDH) system (PermaHeat 100°C, 2 h).[5]

Purity: The selected purification processes isolate the VWF/FVIII complex under conditions that protect the protein structure, resulting in an approximately 1:1 ratio of VWF:RCo (ristocetin cofactor) and FVIII activities. No albumin is added as a stabilizer.[5]

Efficacy & Tolerability: Pharmacokinetic properties, efficacy, and tolerability have been demonstrated in prospective clinical studies in patients with VWD.[5]

Availability: wilate® is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following two vial strengths:

rapidly dissolved in a small injection volume, may help save time during administration.

- **450 IU VWF:RCo and 450 IU FVIII activities in 5 mL**
- **900 IU VWF:RCo and 900 IU FVIII activities in 10 mL[5]**

Photos are of models and for illustrative purposes only.

Important Safety Information

wilate® is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes 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. Clinical trials to evaluate the safety and efficacy of prophylactic dosing with wilate® to prevent spontaneous bleeding have not been conducted in VWD subjects. wilate® is not indicated for the prevention of excessive bleeding during and after surgery in patients with VWD. wilate® is not indicated for Hemophilia A.

wilate® is contraindicated for patients who have known anaphylactic or severe systemic reaction to plasma-derived products, any ingredient in the formulation, or components of the container.

Hypersensitivity or allergic reactions have been observed upon use of wilate® and may in some cases progress to severe anaphylaxis (including shock) with or without fever.

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity. Monitor plasma levels of VWF:RCo and FVIII activities in patients receiving wilate® to avoid sustained excessive VWF and FVIII activity levels, which may increase the risk of thrombotic events.

Patients with VWD, especially type 3 patients, may potentially develop neutralizing antibodies (inhibitors) to VWF, manifesting as an inadequate clinical response. Since inhibitor antibodies may occur concomitantly with anaphylactic reactions, patients experiencing an anaphylactic reaction should also be evaluated for the presence of inhibitors.

wilate® is made from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, eg, viruses and, theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent or other unknown infectious agents, cannot be completely eliminated. Despite measures to reduce this risk, such products may still potentially transmit disease.

The most common adverse reactions to treatment with wilate® in patients with VWD have been urticaria and dizziness. The most serious adverse reactions to treatment with wilate® in patients with VWD have been hypersensitivity reactions.

Please see full prescribing information on the inside back cover.

To report suspected adverse reactions, contact:

Octapharma USA Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch.

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Please see full Prescribing Information.

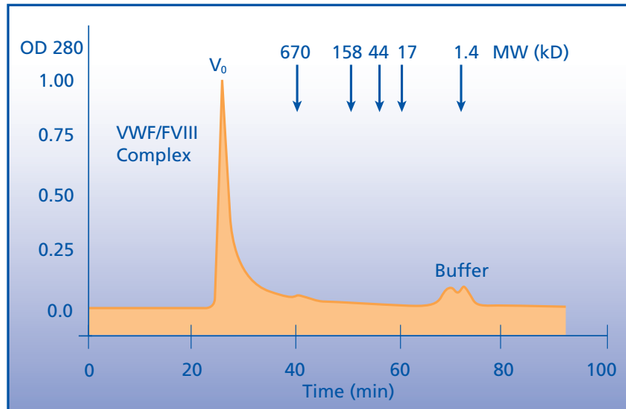
wilate®: Purity

High purity VWF/FVIII complex: Balanced content of active components

The selected purification processes for wilate® isolate the VWF/FVIII complex under conditions that protect the protein structure, resulting in an approximately physiologic 1:1 ratio of VWF:RCo (ristocetin cofactor) and FVIII activities.[5]

The ratio of von Willebrand activity (VWF:RCo) to factor VIII activity (FVIII:C) of approximately 1:1 corresponds to the ratio in normal plasma. Natural hemostasis is based on the interaction between VWF and FVIII. Especially in the case of acute bleeding in VWD patients, the administration of FVIII, in addition to the substitution of VWF, is imperative for rapid cessation of bleeding.[6,7]

wilate® demonstrates one peak on chromatographic separation[8]



Analytical size exclusion chromatography (detection: 280 nm) of wilate® lot.

On chromatographic separation by molecular size, wilate® exhibits a single peak containing only factor VIII and VWF.[8] There is no evidence of other impurities, such as albumin (stabilizer).

Accompanying plasma proteins are efficiently removed

wilate® exhibits high purity. The purification level of clotting factors is defined as specific activity, or the amount of the desired clotting factor per mg of total protein.[9] High purity has been defined as a specific activity of 1-100 units/mg protein for FVIII.[10] The specific activity for wilate® is ≥60 IU VWF:RCo and ≥60 IU FVIII activities per mg of total protein. Actual mean specific activity for both VWF:RCo and FVIII averaged >100 IU/mg total protein for each, suggesting a high purity concentrate.[8] **No albumin is added as a stabilizer.**[5]

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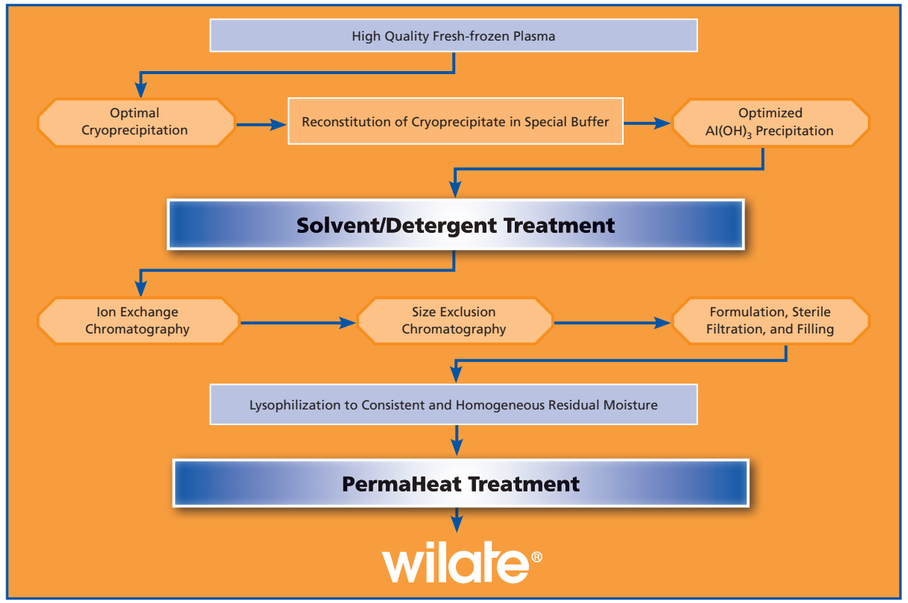
Please see full Prescribing Information.

Manufacturing process

The manufacturing of wilate® involves extensive purification and virus inactivation processes. High quality fresh-frozen plasma undergoes optimal **cryoprecipitation,** which is then reconstituted in a special buffer. The resulting supernatant is incubated under continuous agitation for ≥4 h at +23°C-28°C with virus inactivation utilizing the **solvent/detergent (S/D)** process (0.3% TNBP and 1% Octoxynol-9 (Triton X-100)). During a subsequent **ion exchange chromatography**, the S/D reagents and impurities pass through the column unbound and are removed at lower ionic strength, while the VWF/FVIII complex is eluted at higher ionic strength. The eluate is then applied onto a size **exclusion chromatography** column and the product fraction is collected, representing the paramount peak. After concentration by **ultra-/diafiltration** the product is **formulated, filled, and lyophilized**. The vials then undergo a second viral inactivation process, a special terminal dry-heating (TDH) system (**PermaHeat** 100°C, 2 h). The residual moisture of each vial is controlled (by near infrared spectrophotometry) both before and after PermaHeat treatment. The product is subjected to **quality control** and finally released for clinical use.[5,8]



Plasma contains VWF and FVIII at very low concentrations. The wilate® manufacturing process is designed to enrich the proportion of VWF/FVIII complex. Other plasma proteins may give rise to clinical side-effects, and proteases could impair the stability of coagulation factors and degrade their natural structure and functionality. Because these proteins, such as the protease ADAMTS13, are efficiently reduced during production,[11] there is no need to add protein stabilizers; therefore, no albumin is added.

wilate® is contraindicated in patients with anaphylactic or severe systemic reaction to plasma-derived products.
As with all plasma-derived products, the risk of transmission of infectious agents cannot be completely eliminated.

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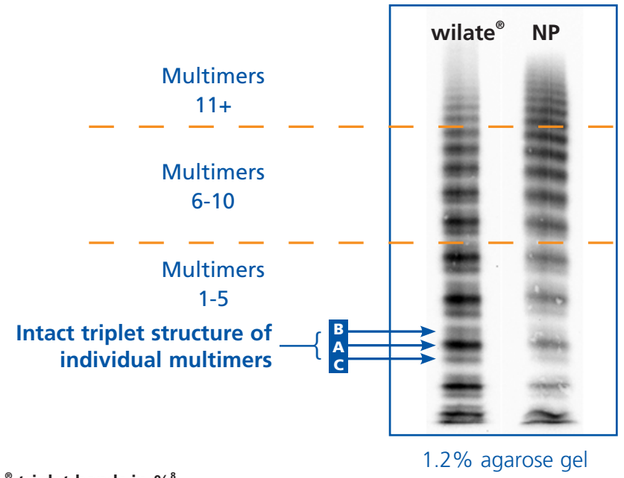
wilate®: VWF Structure

VWF structure compared to human plasma

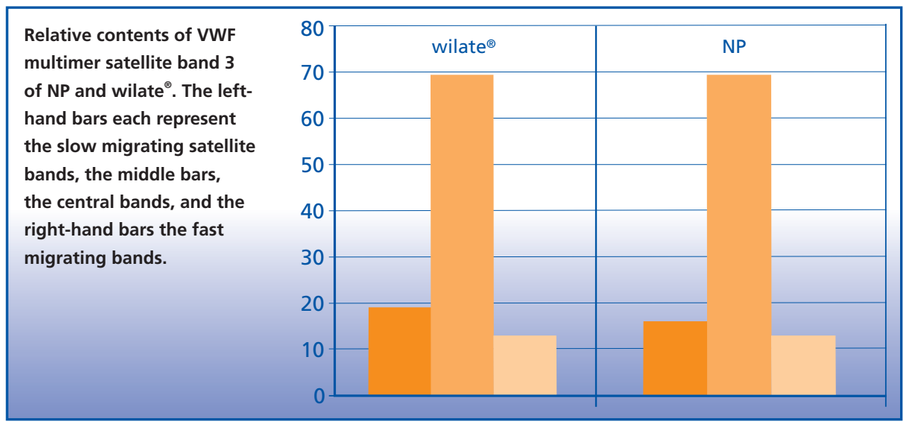
Triplet structure: VWF is present in plasma in the form of various large molecules called VWF multimers. Each individual multimer band consists of three bands that form a triplet. The subbands are of different intensity. Typically in a normal circulating VWF, there is a more pronounced central band (A) and two weaker satellite bands (B, C). A modified abnormal triplet pattern indicates increased breakdown of the VWF.[7,12]

wilate® demonstrated a physiologic triplet structure and multimeric distribution.[8]

Multimer analysis showing triplet structure of wilate® and normal plasma (NP)[11]



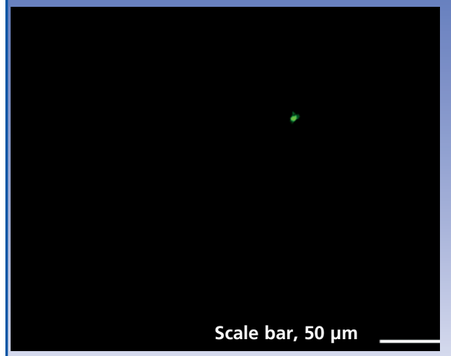
Distribution of wilate® triplet bands in %[8]



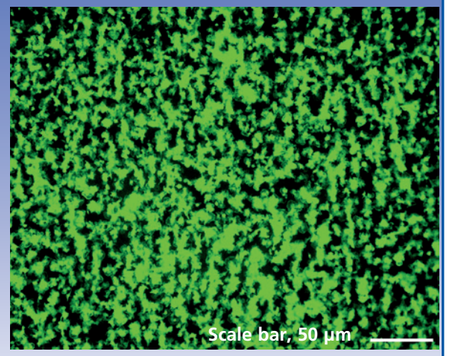
Platelet binding under flow conditions

In a human body, VWF has to exert its haemostatic function under flow conditions. Octapharma is performing VWF studies not only under static conditions but also in a shear rate environment mimicking the physiologic conditions of a blood flow. These experiments clearly demonstrate the ability of wilate® to mediate platelet binding to collagen under shear stress, as found in the vascular system.[13]

VWF-mediated platelet binding to collagen under physiologic flow conditions



Platelet binding to collagen III without substitution of VWF



Platelet binding to collagen III with 1 IU/mL wilate®

Flow conditions (1700 s-1, simulating arterial flow conditions) in presence of washed red blood cells.

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wilate®: Viral Safety

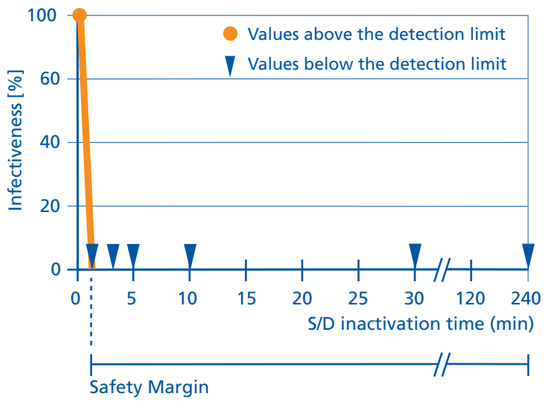
Double virus inactivation:
Solvent/detergent process (TNBP/Octoxynol-9)

Solvent/detergent (S/D) process sets benchmarks in every aspect of effective virus elimination/inactivation. Although a number of viral inactivation steps have been shown to greatly enhance the safety of hemophilia products, S/D process is the current gold standard for safety from the highly infectious enveloped viruses.[9]

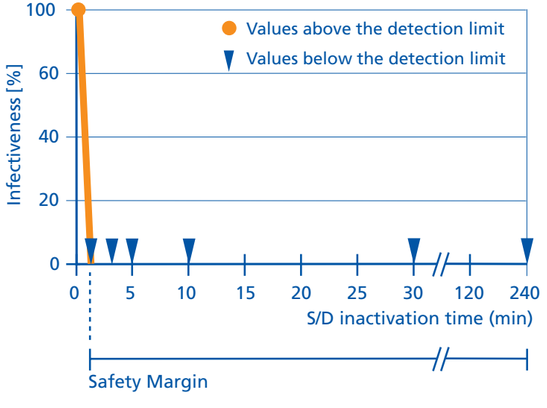
Octapharma was the first manufacturer to apply the S/D process to a large-scale production of FVIII concentrate. The reaction mixture destroys the lipid membrane of the viruses. Lipid-coated viruses, such as HIV, HBV, HCV, and WNV, are destroyed rapidly, effectively, and irreversibly.

Since the introduction of the S/D process, no infections with HIV, HBV, HCV, and WNV or other lipid-coated viruses have been associated with S/D treated products. The viruses used in virus validation studies were selected to represent a broad spectrum of different physical-chemical properties and differing resistance to inactivation processes.

Solvent/detergent inactivation kinetics of Sindbis virus [8,14]



Solvent/detergent inactivation kinetics of HIV [8,14]

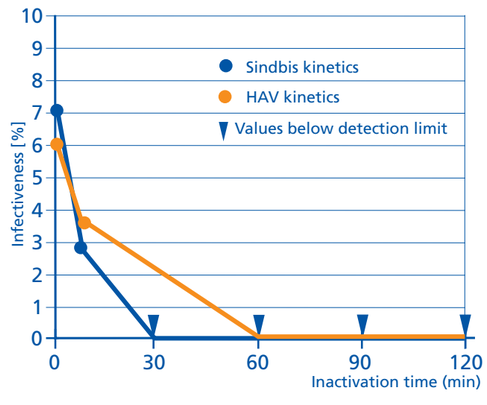


Double virus inactivation:
PermaHeat

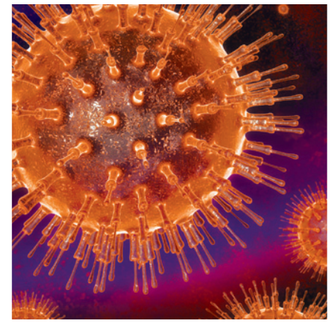
PermaHeat is an optimized heat inactivation process that was developed to supplement the solvent/detergent (S/D) process. PermaHeat treatment (100°C, 2 h) inactivates a broad spectrum of both lipid-coated and non-lipid-coated viruses. All tested viruses are inactivated by at least 4 logs. This also applies to porcine parvovirus, which is known to be very heat resistant, more so than the human parvovirus B19.[11]

The total efficacy of the double viral inactivation process (without taking into account other process steps) is over 10 logs for lipid-coated viruses and more than 6 logs for non-lipid-coated viruses.[5,11]

PermaHeat inactivation kinetics of HAV and Sindbis virus[8,14]



Safety margin through PermaHeat treatment



As with all plasma-derived products, the risk of transmission of infectious agents cannot be completely eliminated. Despite measures to reduce this risk, such products may still potentially transmit disease.

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wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

wilate®: Viral Safety

High removal capacity of prions

It is important to note that the presence of prion pathogens in human plasma, which is used as a starting material in the production of these concentrates, has never been documented. In a study where scrapie prions were added to human plasma, the wilate® manufacturing process has been shown to efficiently remove the prions with a high safety margin. The cumulative prion removal capacity was determined to be 4.2 log.[15, 16]

Calculations show that even under a theoretical assumption that each administered batch contains prions, a patient would need to be regularly treated with wilate® for more than 1200 years before approaching a theoretical risk of prion infection.[16]

Prion removal capacity of the wilate® manufacturing process[15,16]

	Prion Removal Capacity [log]
Sequential protein precipitation steps	1.8
Sequential chromatography steps	2.4
Total	4.2

Virus reduction during the wilate® manufacturing process[5]

Production step	Virus reduction factor [log_{10}]						
	Enveloped viruses				Non-enveloped viruses		
	HIV-1	SBV	BVDV	PRV	REO 3	HAV	PPV
S/D treatment	>7.5	>8.6	>4.2	>8.5	na	na	na
Ion-exchange chromatography	nd	nd	nd	nd	1.9 - 2.3	1.2 – 1.9	3.3
TDH treatment	4.9 - >5.8	>5.5	nd	4.0 - 4.9	>6.4	>5.7	2.6 - 4.1
Global reduction factor	>12.4 - >13.3	>14.1	>4.2	>12.5 - >13.4	>8.3 - >8.7	>6.9 - >7.6	5.9 - 7.4

na = not applicable;
nd = not done (S/D reagents present);
HIV-1 = Human Immunodeficiency Virus – 1;
SBV = Sindbis Virus;
BVDV = Bovine Viral Diarrhea Virus;
PRV = Pseudorabies Virus;
REO 3 = Reovirus Type 3;
HAV = Hepatitis A Virus;
PPV = Porcine Parvovirus

As with all plasma-derived products, the risk of transmission of infectious agents cannot be completely eliminated.

wilate®: Pharmacokinetics

Parallel pharmacokinetic profiles of FVIII and VWF may help facilitate dosing and monitoring

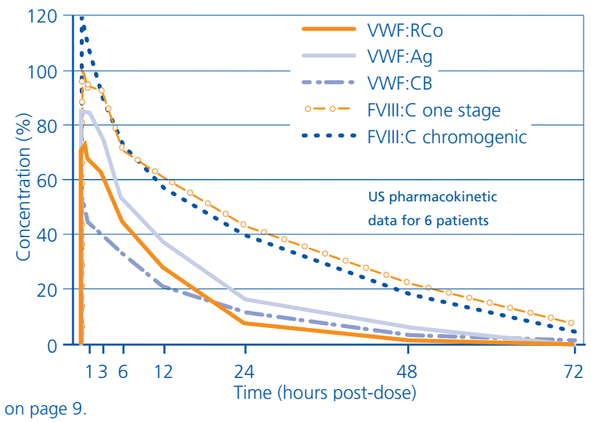
Pharmacokinetic properties are an important consideration with multi-component therapeutic agents, such as VWF/FVIII concentrates. Each of the two components, VWF and FVIII, plays an important role in hemostasis. The physiologic 1:1 ratio in the concentrate, the similar recovery values, and the parallel decay curves for VWF and FVIII in wilate® may help facilitate dosing and monitoring.

Pharmacokinetic parameters of VWF and FVIII in wilate®[5]

Parameters	VWF:RCo: mean ± SD		FVIII:C: mean ± SD – chromogenic	
	VWD type 3 (n=6)	VWD Total (n=20)	VWD type 3 (n=6)	VWD Total (n=19*)
C_{max} (IU/dL)	79 ± 13	76 ± 15	120 ± 23	112 ± 23
AUC(0-inf) (IUhr/dL)	995 ± 292	1235 ± 637	2670 ± 854	2290 ± 1045
Half-life (h)	9.1 ± 2.6	15.8 ± 11.0	16.1 ± 3.1	19.6 ± 6.9
CL (mL/h/kg)	4.2 ± 1.4	3.7 ± 1.5	2.0 ± 0.6	2.9 ± 2.1
Vss (mL/kg)	49.4 ± 16.7	69.7 ± 33.2	44.2 ± 10.4	72.4 ± 36.2
MRT (h)	11.9 ± 2.9	17.4 ± 4.5	23.0 ± 3.7	28.4 ± 11.1
Recovery (%IU/kg)	2.1 ± 0.3	2.0 ± 0.5	2.5 ± 0.5	2.2 ± 0.5

*One subject with implausible long half-life is not included in the summary table, except for recovery result. C_{max} = peak concentration; AUC = area under curve; CL = clearance; Vss = volume of distribution at steady state; MRT = mean residence time

Median dose-adjusted concentrations vs time in patients with VWD type 3[11,17]



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wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

wilate®: Efficacy

wilate® efficacy assessed using an additional set of stringent objective criteria

The efficacy of wilate® in the treatment of bleeding episodes was analyzed using both the traditional subjective 4-point hemostatic efficacy scale (excellent, good, moderate, and none) and an **additional** set of objective criteria. In fact, wilate® is the first VWF/FVIII complex to be evaluated by the FDA using both subjective and objective criteria to determine efficacy. **The treatment of a bleeding episode was classified as a success only if all of the objective criteria were fulfilled.**[5]

wilate® objective efficacy criteria: a high standard for success

Treatment of a bleeding episode was rated "successful" only if ALL criteria were fulfilled:

- Last efficacy rating of the bleeding episode was "excellent" or "good"
- Episode was NOT additionally treated with another VWF-containing product (excluding whole blood)
- Patient did NOT receive a blood transfusion during the episode
- Follow-up treatment with a daily dosage of wilate® that was ≤50% of the initial dose (for bleeding episodes with more than 1 day of treatment)
- Treatment duration of <4 days in cases of severe bleeding (other than gastrointestinal)
- Treatment duration of <3 days in cases of moderate bleeding (other than gastrointestinal)
- Treatment duration of <2 days in cases of minor bleeding (other than gastrointestinal)

The most common adverse reactions to treatment with wilate® in patients with VWD have been urticaria and dizziness. The most severe adverse reactions have been hypersensitivity reactions.

Photos are of models and for illustrative purposes only.

Proven clinical efficacy in the treatment of acute bleeds*

Clinical efficacy of wilate® in the control of bleeding in patients with VWD was evaluated in four prospective clinical studies. Data were obtained from 70 VWD patients, of which 37 were type 3. Among the 70 VWD patients, 45 received on-demand treatment for bleeding episodes.[5]

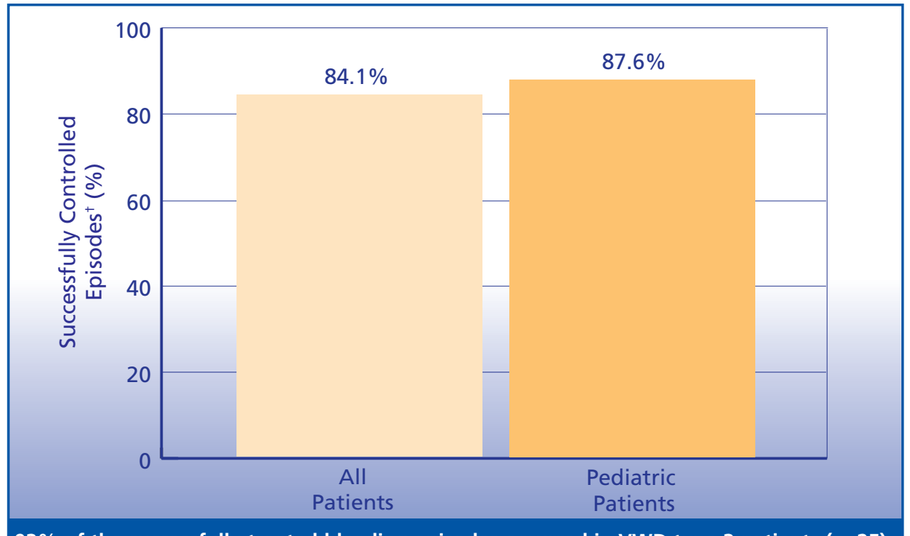
Using the objective criteria, 84% of the bleeding episodes† were rated as being successfully treated. The most common bleeding sites were joints, followed by epistaxis, GI tract, gynecologic, and oral.[5]

The majority of bleeding episodes were treated for 1-3 days. In patients with GI bleeds, the duration for product use to control bleeding could be much longer (up to 7 days).[5]

Pediatrics: Proven clinical efficacy in the treatment of acute bleeds*

As part of the prospective clinical studies, 234 bleeding episodes† in 11 pediatric patients (5-16 years of age), of whom 73% were type 3 VWD, were treated with wilate®. Using objective criteria, the overall haemostatic efficacy of wilate® was rated as successful in 88% of acute bleeding episodes. The most common bleeding sites were joints, followed by gynecologic, epistaxis, oral, and GI tract.[5]

Efficacy in all patients and pediatric patients with VWD analyzed by objective criteria[5]



93% of the successfully treated bleeding episodes occurred in VWD type 3 patients (n=25).

*In patients with severe VWD as well as patients with mild to moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

†A "bleeding episode" may involve bleeding at multiple sites in this analysis.

Please see Important Safety Information on page 9.
Please see full Prescribing Information.

wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

wilate®: Tolerability

Incidence of adverse reactions

In clinical trials including 92 VWD patients who received 5676 wilate® infusions, the most common adverse reactions were urticaria and dizziness (each with 2 patients; 2.2%). The most serious adverse reactions reported with wilate® use have been hypersensitivity reactions.[5]

Post-marketing adverse reactions reported in patients treated for VWD include hypersensitivity reactions, dyspnea, nausea, vomiting, and cough.

No drug interactions with other medicinal products have been reported with wilate®.

No reported thrombotic events in pre-approval clinical trials[11]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity. Monitor plasma levels of VWF:RCo and FVIII activities in patients receiving wilate® to avoid sustained excessive VWF and FVIII activity levels, which may increase the risk of thrombotic events.

In clinical trials including 92 VWD patients who received 5676 wilate® infusions, there were four patients (4.4%) who showed seroconversion for antibodies to parvovirus B19 not accompanied by clinical signs of disease. Seroconversion has not been reported since implementation of minipool testing of plasma used for the manufacture of wilate®.

Photos are of models and for illustrative purposes only.

wilate®: Special Populations

Pregnancy/nursing

wilate® has been designated Pregnancy Category C. Animal reproduction studies have not been conducted with wilate®. It is also not known whether wilate® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. wilate® should be given to a pregnant woman only if clearly needed. wilate® has not been studied in labor or delivery or in lactating women. It should be administered to VWF-deficient women at labor or delivery only if clearly indicated.[5]

Pediatric use

Eleven pediatric patients with VWD between 5 to 16 years of age (8 type 3, 1 type 2, 2 type 1) were treated with wilate® for 234 bleeding episodes in clinical studies. These studies showed that 88% of the bleeding episodes were treated successfully in this population. No dose adjustment is needed for pediatric patients as administered dosages were similar to those used in the adult population.[5]

Geriatric use

Although some of the patients who participated in the wilate® studies were over 65 years of age, the number of patients was inadequate to allow subgroup analysis to support recommendations in the geriatric population.[5]

Please see Important Safety Information on page 9.
Please see full Prescribing Information.

wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

wilate®: Dosing

Convenient dosing interval: 12-24 hours

Simple dosage calculation

The balanced 1:1 ratio of VWF:RCo and FVIII:C in wilate® may facilitate dosage calculation in VWD therapy, based on the declared units (vial sizes of 450 or 900 IU). Thus, differentiation according to FVIII:C or VWF:RCo is not required.

In clinical trials demonstrating the efficacy of wilate® in the control of trauma induced/spontaneous bleeds, the dosing regimens shown in the table were used, which included convenient 12 - 24 hour dosing schedules. The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with GI bleeds, higher doses may be required.[5]

wilate® dosing for treatment of minor and major hemorrhages for all VWD types[5]

Type of hemorrhages	Loading dosage (IU VWF: RCo/kg BW)	Maintenance dosage (IU VWF: RCo/kg BW)	Therapeutic goal
Minor hemorrhages	20-40 IU/kg	20-30 IU/kg every 12-24 hours*	VWF:RCo and FVIII activity trough levels of >30%
Major hemorrhages	40-60 IU/kg	20-40 IU/kg every 12-24 hours*	VWF:RCo and FVIII activity trough levels of >50%

*This may need to be continued for up to 3 days for minor hemorrhages and 5-7 days for major hemorrhages.

Physician supervision of the treatment regimen is required. The careful control of replacement therapy is especially important in life-threatening hemorrhages. When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity, which may increase the risk of thrombotic events.

Photos are of models and for illustrative purposes only.

wilate®: Convenience/Storage

Rapidly dissolved in a small injection volume

wilate® is rapidly dissolved in a small injection volume (450 IU in 5 mL, 900 IU in 10 mL) to help ease handling and administration for doctors, nurses, and patients.

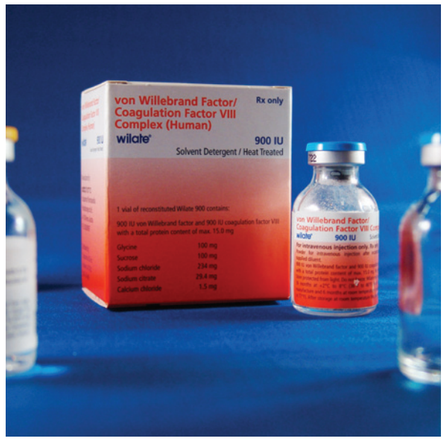
Reconstitute wilate® powder only directly before injection, use the solution immediately on one occasion only, and discard any remaining solution.[5]

Two convenient vial sizes

wilate® is supplied in a package with a single-dose vial of lyophilized powder and a vial of diluent (Water for Injection with 0.1% Polysorbate 80), together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set, and two alcohol swabs.[5]

Each vial of wilate® contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay. Components used in the packaging of wilate® contain no latex.[5]

NDC Number	Size
67467-181-01	450 IU VWF:RCo and 450 IU FVIII activities in 5 mL
67467-181-02	900 IU VWF:RCo and 900 IU FVIII activities in 10 mL



Storage

wilate® can be stored for up to 36 months in a refrigerator (+2°C to +8°C or 36°F to 46°F) protected from light from the date of manufacture. During this period, wilate® may be stored for up to 6 months at room temperature (maximum of +25°C or 77°F).[5]

Do not freeze. Do not use after the expiration date. Store in the original container to protect from light.[5]

Please see Important Safety Information on page 9.
Please see full Prescribing Information.

wilate®: Summary

wilate®: Developed specifically for the treatment of patients with von Willebrand disease

VWF quality and purity

wilate® is derived exclusively from large pools of human plasma collected in US FDA-certified plasma donation centers. The selected purification processes isolates the VWF/FVIII complex under conditions that protect the protein structure. No albumin is added as a stabilizer.[5]

Double virus inactivation

wilate® is a double virus inactivated VWF/FVIII, utilizing the solvent/detergent (S/D) process (0.3% TNBP, 1.0% Octoxynol-9) and a special TDH system (PermaHeat 100°C, 2 h).[5] The total efficacy of the double viral inactivation process (without taking into account other process steps) is over 10 logs for lipid-coated viruses and more than 6 logs for non-lipid-coated viruses.[5,11]

Physiologic 1:1 ratio of VWF and FVIII

The balanced 1:1 ratio of VWF:RCo (ristocetin cofactor) and FVIII activities in wilate® corresponds to that seen in normal plasma.[5]

Parallel pharmacokinetic profiles for FVIII and VWF

The similar recovery values, parallel decay curves, and physiologic 1:1 ratio of VWF and FVIII in wilate® may help facilitate dosing and monitoring.[5]

Clinical efficacy in adult and pediatric populations

Clinical efficacy of wilate® in patients with VWD was determined in four prospective clinical studies, including 92 VWD patients who received more than 5670 wilate® infusions. Among 70 VWD adult patients, 45 patients received on-demand treatment for 1068 bleeding episodes. Using an **additional** set of objective efficacy criteria, 84% of the bleeding episodes were rated as being successfully treated. In these 45 patients, 93% of the successfully treated episodes were in patients with type 3 VWD (n=25). Among 11 pediatric patients (5-16 years of age), treated for 234 bleeding episodes, 88% were rated as being successfully treated, using objective criteria.[5]

Tolerability

In wilate® clinical trials, the most common adverse reactions were urticaria and dizziness (each with 2 patients; 2.2%).[5] The most serious adverse reactions to treatment with wilate® in patients with VWD have been hypersensitivity reactions.[5]

Rapidly dissolved in a small injection volume

wilate® is rapidly dissolved in a small injection volume (450 in 5 mL, 900 IU in 10 mL),[5] to help ease handling and administration for doctors, nurses, and patients.[5]

Convenient dosing and administration

The balanced 1:1 ratio of VWF:RCo and FVIII:C in wilate® may facilitate dosage calculation in VWD therapy, based on the declared units (vial sizes of 450 or 900 IU). Thus, differentiation according to FVIII:C or VWF:RCo is not required.[5] In clinical trials demonstrating the efficacy of wilate®, dosing regimens included convenient 12 - 24 hour dosing schedules.

Photos are of models and for illustrative purposes only.

Please see Important Safety Information on page 9.
Please see full Prescribing Information.

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wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

Developed Specifically for the Treatment of Patients with von Willebrand Disease

- **High purity VWF/FVIII complex**
- **Double virus inactivation**
- **Physiologic 1:1 ratio of VWF and FVIII**
- **Parallel pharmacokinetic profiles for FVIII and VWF**
- **Clinical efficacy, safety, and tolerability proven in adult and pediatric populations**
- **Rapidly dissolved in a small volume**
- **Convenient dosing interval**

Contraindicated in patients with anaphylactic or severe systemic reaction to plasma-derived products or formulation ingredients.

Please see Important Safety Information on page 9.

Please see full Prescribing Information.

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For the safe and optimal use of human proteins