



wilate®

New Generation
VWF/FVIII
Concentrate

Developed to Set New Standards
in VWD Treatment

octapharma

For the safe and optimal use of human proteins

Plasma is a Matter of Trust

Octapharma establishes worldwide benchmarks

The idea of producing a solvent/detergent (S/D) virus inactivated factor VIII concentrate was the starting point for the company's founding in 1982. Octapharma was the first company in the world to introduce the solvent/detergent process for virus inactivation on an industrial scale in the production of a factor VIII concentrate.

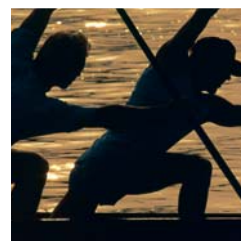
After more than 20 years of experience in the development of coagulation products, Octapharma has become a global company with a comprehensive portfolio of plasma products. Today, Octapharma specializes not

only in coagulation products for the treatment of haemophilia, but also in immunology, transfusion medicine and intensive care.

Innovative products that establish new benchmarks in terms of handling, safety and efficacy are Octapharma's primary focus. Currently, patients in over 70 countries around the world are treated with Octapharma products. Five fully integrated production sites in Austria, France, Sweden, Germany and Mexico guarantee that Octapharma customers benefit from the safest possible product supply.

wilate®

**New Generation
VWF/FVIII
Concentrate**



wilate® – Quality Requirements Completely Redefined

New generation concentrate for VWD patients

wilate® is a newly developed, high-purity, double virus inactivated VWF/FVIII concentrate. It is indicated for the treatment and prophylaxis of all types of von Willebrand disease (VWD) and in classic and acquired haemophilia A.

wilate® is the first double virus inactivated, high purity concentrate developed specifically for von Willebrand disease patients.

Using the solvent/detergent process (0.3% TNBP, 1.0% Octoxynol-9) and a special terminal dry-heating system (PermaHeat 100 °C, two hrs.) two effective virus inactivation processes are combined.

The selected purification processes isolate the VWF/FVIII complex under conditions that maximally protect the protein structure. wilate® exhibits very high purity for both factors, VWF and FVIII. As a result, the physiological function and ratio between the two factors are preserved.

Prospective clinical studies demonstrate that wilate® has outstanding pharmacokinetic properties, very good efficacy and excellent tolerability.

wilate® is rapidly dissolved in a small injection volume, thus saving time during administration.

wilate® at a glance

- Double virus inactivated
- VWF quality close to normal plasma
- High purity for excellent tolerability
- VWF and FVIII in a physiological ratio of 1 to 1
- Excellent clinical efficacy and tolerability
- Rapidly dissolved in a small volume



wilate®	
wilate® 450 IU	in 5 ml
wilate® 900 IU	in 10 ml



High Purity for High Quality von Willebrand Factor

Accompanying plasma proteins are efficiently removed

wilate® exhibits very high purity. Plasma contains VWF and FVIII at very low concentration. The wilate® manufacturing process is designed to enrich the proportion of VWF/FVIII complex. Accompanying plasma proteins that may give rise to clinical side-effects, as well as proteases that could impair the stability of coagulation factors and degrade their natural structure and functionality, are efficiently removed during production. This makes the addition of protein stabilizers superfluous. Specific activity for FVIII:C averaged 122 IU/mg total protein and 101 IU/mg total protein for VWF:RCO.^{1,2,3} These properties explain why wilate® exhibits such excellent tolerability.^{4, 5, 6, 7}

Balanced content of active components and maintenance of physiological functions

The selected purification processes isolates the VWF/FVIII complex under highly protein-protecting conditions. wilate® contains both components of the VWF/FVIII complex in a physiological form. This is shown by the ratios of protein quantity to function, which are close to 1.

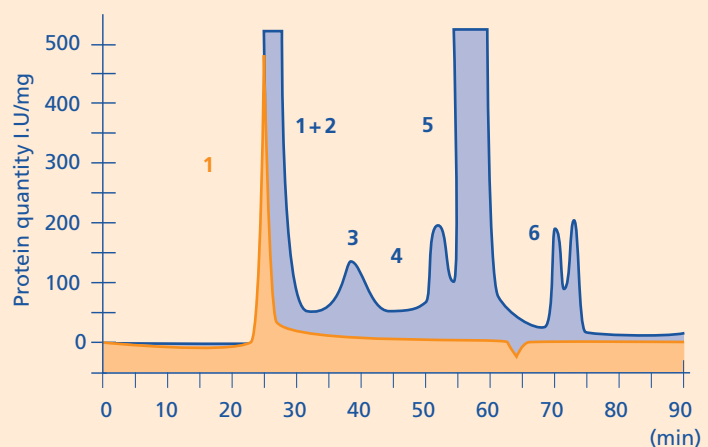
FVIII:Ag/FVIII:C	1.2
VWF:Ag/VWF:RCO	1.1
VWF:Ag/VWF:CB	1.0

This means that the protein function remains preserved.^{2, 3}

wilate®

**High Purity for
Excellent Efficacy
and Tolerability**

Chromatographic separation by molecular size³



1: wilate® contains high purity VWF/FVIII complex

Comparison preparation

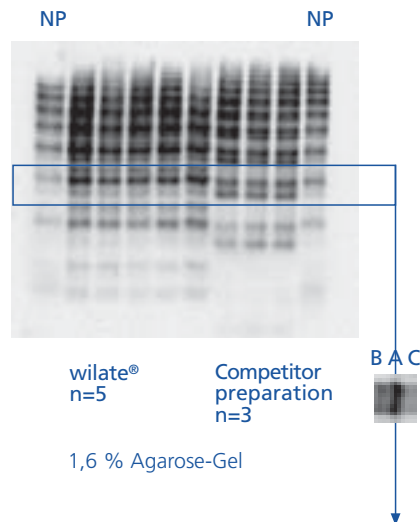
1: VWF/FVIII complex; 2: High molecular weight impurities;
3: Fibrinogen, Immunoglobulins; 4: Albumin dimer;
5: Albumin monomer; 6: Stabilisers

The ratio of factor VIII activity (FVIII:C) to von Willebrand activity (VWF:RCO) of almost 1 also corresponds to the ratio in normal plasma. Natural haemostasis 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.^{8, 9}

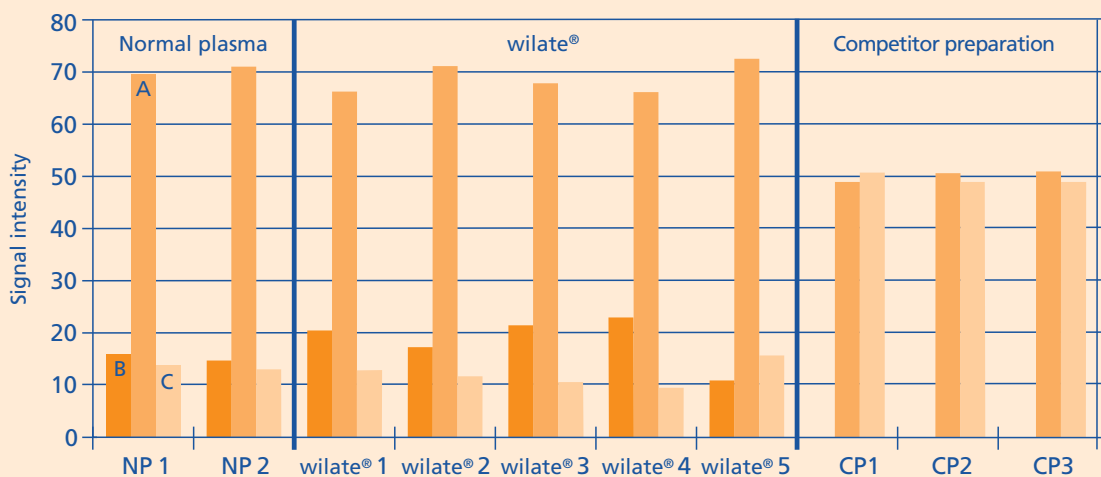
Physiological triplet structure

VWF is present in plasma in the form of various large molecules, the so-called VWF multimers. Each individual multimer band consists of three bands that form a triplet. The sub-bands 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.^{9, 10}

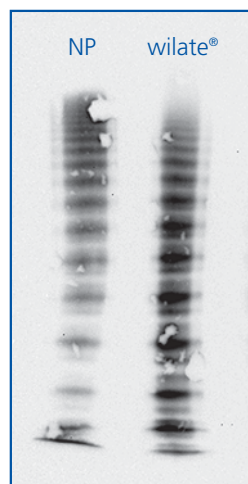
Multimer analysis on a 1.6 % agarose gel shows that wilate® exhibits a physiological triplet structure that are similar to normal plasma (NP).



Distribution of triplet bands in %



wilate® has a physiological VWF pattern that corresponds to that of normal plasma. The modified triplet pattern in the comparison product suggests increased VWF proteolysis.



VWF multimeric distribution close to normal plasma

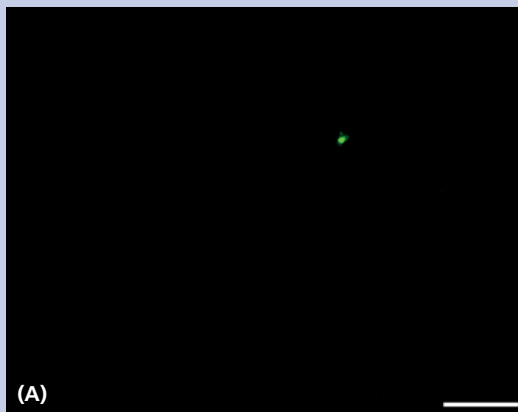
Multimeric analysis on a 1.2% agarose gel shows that the multimeric distribution of VWF in wilate® resembles that of normal human plasma (NP).



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 physiological 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.¹¹

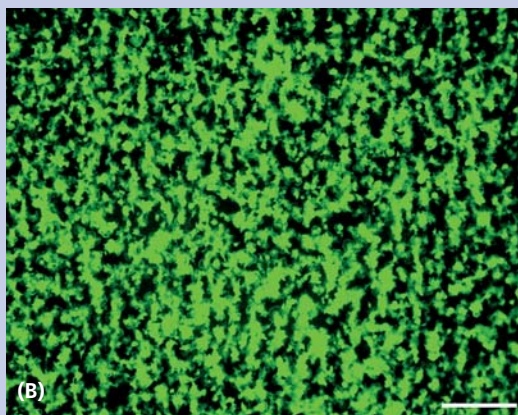
wilate®

**High Purity for
High Quality VWF**



VWF-mediated platelet binding to collagen under physiological flow conditions (1700 s^{-1} , simulating arterial flow conditions) in presence of washed red blood cells.*

(A) Platelet binding to collagen III without substitution of VWF.



(B) Platelet binding to collagen III with 1 IU/mL wilate®. Scale bar, 50 μm

wilate® is very well tolerated⁷

In clinical trials, in total, > 99% of more than 5300 infusions were rated as “very good” or “good” in terms of tolerability.

Double Virus Inactivation that Sets Benchmarks

The special S/D inactivation (TNBP/Octoxynol-9)

Since the mid-1980s, the requirements for the viral safety of plasma preparations have constantly been made more and more stringent. For each preparation it must be demonstrated that the manufacturing process guarantees sufficiently effective virus elimination / inactivation.^{12, 13}

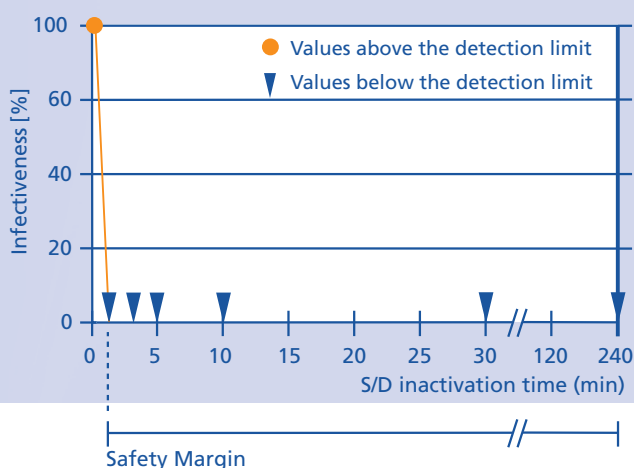
S/D inactivation sets benchmarks in every respect. While a number of viral inactivation steps have been shown to greatly enhance the safety of haemophilia products, S/D inactivation is the current gold standard for safety from the highly infectious enveloped viruses.¹⁴

Octapharma was the first manufacturer to apply the S/D inactivation to a large-scale production of plasma derivatives. This process has been used in all Octapharma coagulation products since 1986. The reaction mixture destroys the lipid membrane of the viruses. Lipid-coated viruses, which include the transfusion-relevant viruses such as HIV, HBV, HCV and WNV, are destroyed very rapidly, effectively and irreversibly.

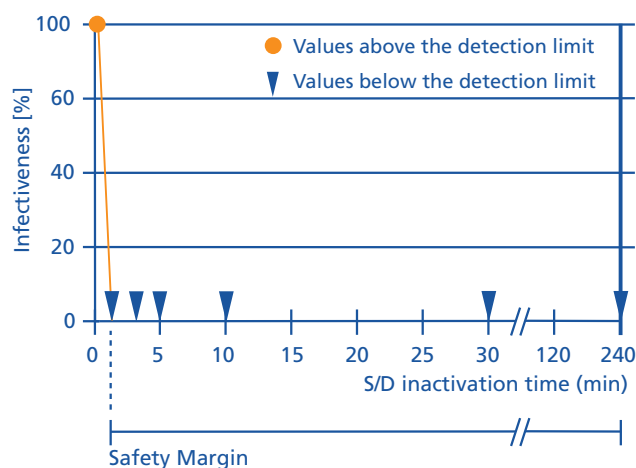


Since the introduction of the S/D inactivation-process, no infections with HIV, HBV, HCV and WNV or other lipid-coated viruses, have been associated with S/D treated products. The viruses used in virus validation studies were selected in such a way that they cover a broad spectrum of different physical-chemical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

A: S/D Inactivation kinetics of Sindbis virus^{2, 15}



B: S/D Inactivation kinetics of HIV^{2, 15}



PermaHeat – the new heat inactivation system

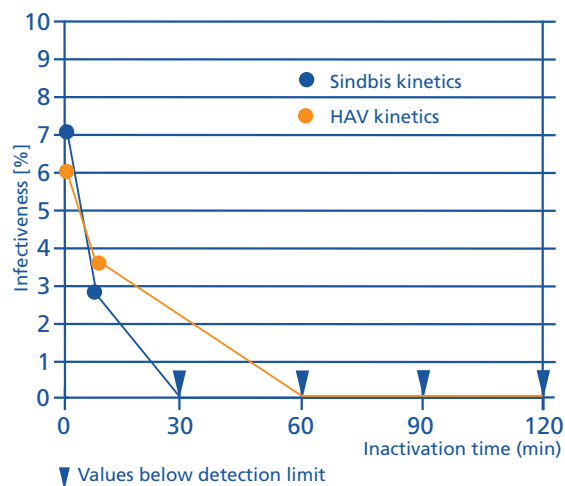
The S/D process – the gold standard for the inactivation of lipid-coated viruses – rapidly and irreversibly destroys viruses such as HIV, HBV, HCV and WNV.¹⁴ An optimised heat inactivation process was developed in order to supplement it. The PermaHeat-treatment (100 °C, 2 hrs) inactivates a broad spectrum 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 than the human parvovirus B19. Thus, the total efficacy of these two virus inactivation processes (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.

wilate®

Double Viral Safety
for VWD Patients

wilate®: Virus inactivation through PermaHeat ^{2, 15}



High safety margin through
PermaHeat treatment

wilate® virus safety¹⁶

	Virus reduction [log]					
Pathogen	HIV	HBV	HCV	WNV	HAV	B19
Model used	HIV-1	PRV	SBV	SBV	HAV	PPV
Ion exchange chromatography	-	-	-	-	1.9	3.3
S/D treatment	≥ 7.5	≥ 8.5	≥ 8.6	≥ 8.6	-	-
PermaHeat treatment	≥ 5.8	4.9	≥ 5.5	≥ 5.5	≥ 5.7	4.1
Total	≥ 13.3	≥ 13.4	≥ 14.1	≥ 14.1	≥ 7.6	7.4

HIV, human immunodeficiency virus;
HBV, hepatitis B virus
HCV, hepatitis C virus

WNV, West-Nile virus
HAV, hepatitis A virus
B19, human parvovirus B19

PRV, pseudorabies virus
SBV, sindbis virus
PPV, porcine parvovirus



wilate® manufacturing process has high prion removal capacity

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.

Even in the hypothetical case of presence of prion proteins in human plasma, the wilate® manufacturing process has a capacity of efficiently removing them with a high safety margin. The cumulative prion removal capacity was determined to be 4.2 log.^{16, 17}

Calculations show that even under an unrealistic theoretical assumption that each administered batch contains prions, a patient would need to be regularly treated with wilate® for more than 1200 years before he may approach a theoretical risk of prion infection.¹⁷



wilate®

Unsurpassed
Pathogen Safety
for VWD Patients

Validated prion removal capacity of the wilate® manufacturing process^{16, 17}

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

Stringent plasma requirements

The safety and quality of plasma products begins with the starting material. Blood collection centres, donors and donated blood are carefully selected and monitored. Octapharma uses only plasma from Germany, Austria, Sweden and the USA to manufacture wilate®. Complete data on our plasma suppliers is included in the dossiers submitted to regulatory authorities and forms part of the product approval.

Every plasma collection centre is thoroughly inspected by Octapharma's Quality Assurance auditors prior to acceptance. Collection centres that do not meet the demanding high standards of our inspection team are rejected until they have implemented the standards necessary for qualification.

Following initial approval, all plasma centres undergo regular ongoing inspections by both Octapharma and the relevant national authorities.

Every donor undergoes extensive medical examination prior to donation.

All donated plasma undergoes individual unit testing for antibodies against HIV-1/2, HBV, HCV. In addition, the plasma undergoes PCR (NAT) testing for HIV, HBV, HCV, HAV and parvovirus B19.

Physiological Pharmacokinetics Documented for wilate®

In prospective clinical trials (haemophilia A and VWD), a total of 152 patients have received more than 10 million IU of wilate® over more than 10,000 treatment days.

In the subset of VWD studies, 84 VWD patients were administered a total of more than 7.5 million IU of wilate® in more than 5300 infusions. In addition to clinical efficacy, safety and tolerability, pharmacokinetic parameters were assessed.

Similar pharmacokinetic profiles for FVIII and VWF

Pharmacokinetic properties are an important consideration when trying to determine the best treatment for the patient. With multicomponent therapeutic agents, such as VWF/FVIII concentrates where each of the two components, VWF and FVIII, plays its own important role in haemostasis, it is desirable that the half-lives of both proteins are close to each other. This way, the risk of underdosing or overdosing of either of the parameters while trying to keep one parameter at a certain range over a period of several days, e.g. in a surgical setting, is minimised.

wilate® pharmacokinetics from prospective study in the US¹⁸

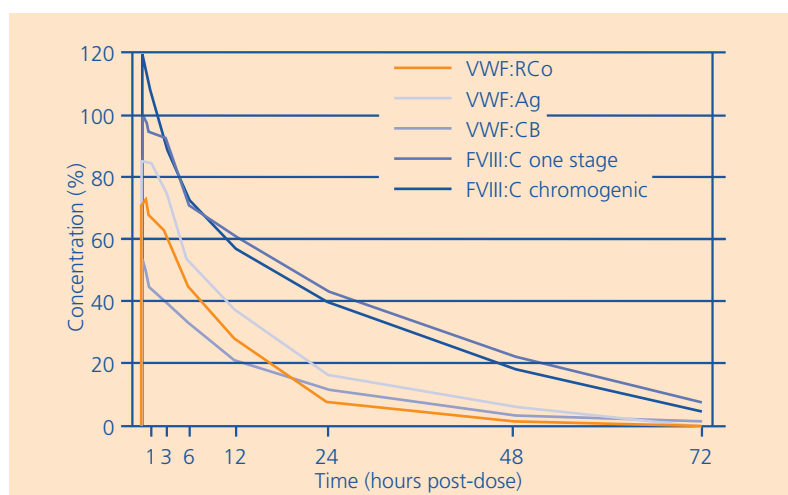
	Average half-life (hrs)
VWD type 3 n=6 / VWF:RCo	12.6
VWD type 3 n=6 / FVIII:C	13.0



As part of the FDA requirements, a pharmacokinetic assessment of both FVIII:C and VWF:RCo in 21 US VWD patients (thereof 6 patients of type 3) has been performed prospectively.¹⁸

The half-lives of FVIII:C and VWF:RCo as determined in VWD type 3 patients are similar. This fact offers a clear safety advantage for the patient: the chance of an accumulation of one of the components and the associated thrombotic risks can be minimized; in addition, underdosing of one component and subsequent bleeding risk is avoided. Together with a physiological 1:1 ratio in the concentrate, similar pharmacokinetic profiles of FVIII and VWF simplify dosing and monitoring – an advantage for the treating physician.

Median values for dose-adjusted concentrations vs. time, VWD type 3, US pharmacokinetic data for 6 patients ^{18, 22}



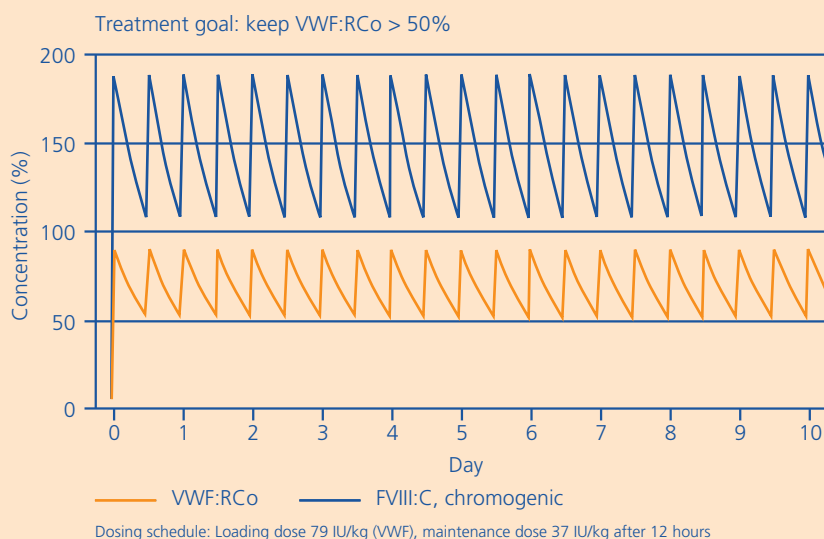
wilate®

Physiological
Pharmacokinetic
Properties

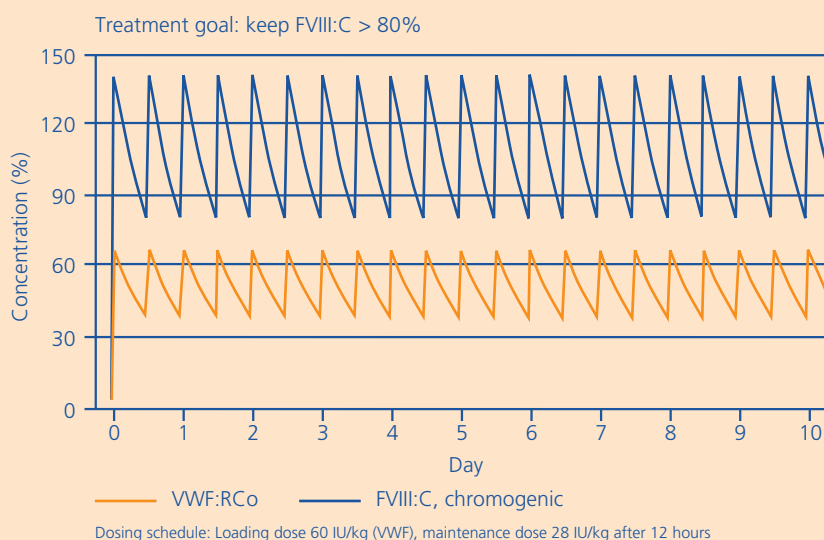
wilate® pharmacokinetics from prospective studies in Europe ⁶

	Recovery (%IU/kg)		Half-life (hrs)	
	wilate®	Normal value	wilate®	Normal value
VWD type 3 patients n=11 / VWF:RCo	1.6	1-2 ¹⁹	17.5	12-20 ²¹
Haemophilia A patients n=12 / FVIII:C	2.0	1-2 ¹⁹	14.8	8-20 ²⁰

Data from pharmacokinetic investigations are available also for 21 VWD patients from European prospective pharmacokinetic studies. 50 IU of wilate® per kg body weight were administered and plasma samples taken up to 72 hours after the infusion. wilate® exhibits outstanding pharmacokinetic properties: in type 3 patients (n=11), the mean half-life for VWF:RCo was 17.5 hours. The mean incremental recovery in these patients was 1.6%/IU/kg body weight for VWF:RCo and 2.0%/IU/kg body weight for FVIII:C. ⁶ Thus, both recovery and half-life are within the physiological range.



Impact of physiological VWF/FVIII ratio and similar half-lives:
Multiple dosing calculations based on the US pharmacokinetic findings for type 3 patients.¹⁸ Even after repeated dosing over 10 days, no FVIII accumulation or insufficient VWF levels are expected.



Proven Clinical Efficacy in the Treatment of Acute Bleeding Episodes⁷

wilate® has been shown to be effective in the treatment of acute bleeds

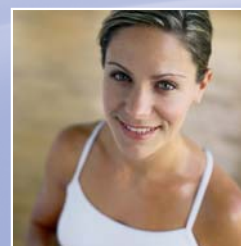
1095 bleeding episodes in VWD patients were successfully treated with a mean dosage of 29 IU/kg body weight after a mean of 1.9 treatment days. Overall the efficacy was subsequently rated by the investigator as "excellent" or "good" in 96 % of treatments.

Efficacy in bleeding episodes⁷

Predominant Site of Bleeding	Number of bleeding episodes	Excellent/Good Efficacy	Mean dose per infusion [IU/kg]
Joints	565	99%	28
Epistaxis	94	94%	27
Gastrointestinal	145	82%	44
Oral	34	94%	26
Gynaecologic	62	97%	36
Other	195	99%	23
Total	1095	96%	29

wilate®

Prospectively Proven Clinical Efficacy



wilate® is effective in pediatric patients with VWD

As part of the prospective clinical studies 212 bleeding episodes in pediatric patients under 12 years of age were treated with wilate®. 75% of the patients were severe VWD type 3 patients. The overall haemostatic efficacy of wilate® was rated as excellent or good in 98% of acute bleeding episodes with a mean dose of 29 IU/kg body weight.

Efficacy in pediatric patients^{7, 22}

Predominant Site of Bleeding	Number of bleeding episodes	Excellent/Good Efficacy	Mean dose per infusion [IU/kg]
Joints	132	100%	30
Epistaxis	31	94%	26
Gastrointestinal	1	100%	22
Oral	26	92%	25
Gynaecologic	10	100%	47
Other	12	100%	25
Total	212	98%	29

wilate[®] is Effective and Safe in Surgical Interventions

Prospectively proven in minor and major surgery²³

In clinical trials, in total 58 surgical procedures have been performed in 33 VWD patients. 27 surgeries were major, including hip replacement and small bowel resection, and the rest of the procedures were related mostly to dental surgery. 67 % of all surgeries were performed in VWD type 3 patients.



In minor surgery, wilate[®]'s haemostatic efficacy was rated as excellent or good in 97% cases. The mean dose per infusion was 37 IU/kg body weight in this patient group, with a mean number of 1.6 infusions.

In major surgeries a mean pre-op loading dose of 48 IU/kg body weight was administered. Mean maintenance dose was 24 IU/kg body weight, with a mean of 10.6 infusions.

Overall, efficacy was rated as excellent or good in 95% cases.

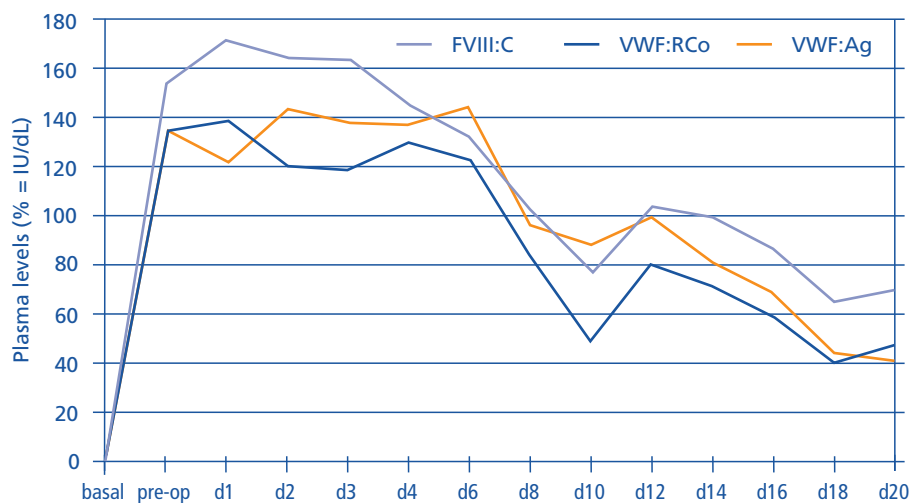
Table: wilate[®] in minor surgery²³

Mean dose per infusion	37 IU wilate [®] /kg
Mean number of infusions	1.6

wilate[®] doses in major surgery²³

Mean loading dose	48 IU wilate [®] /kg
Mean maintenance dose	24 IU wilate [®] /kg
Mean total dose per infusion	31 IU wilate [®] /kg
Mean number of infusions	10.6

No accumulation of FVIII or VWF even after multiple dosing.
Case example 1: wilate® in a total knee replacement in a VWD type 3 patient, 56y, female²⁴

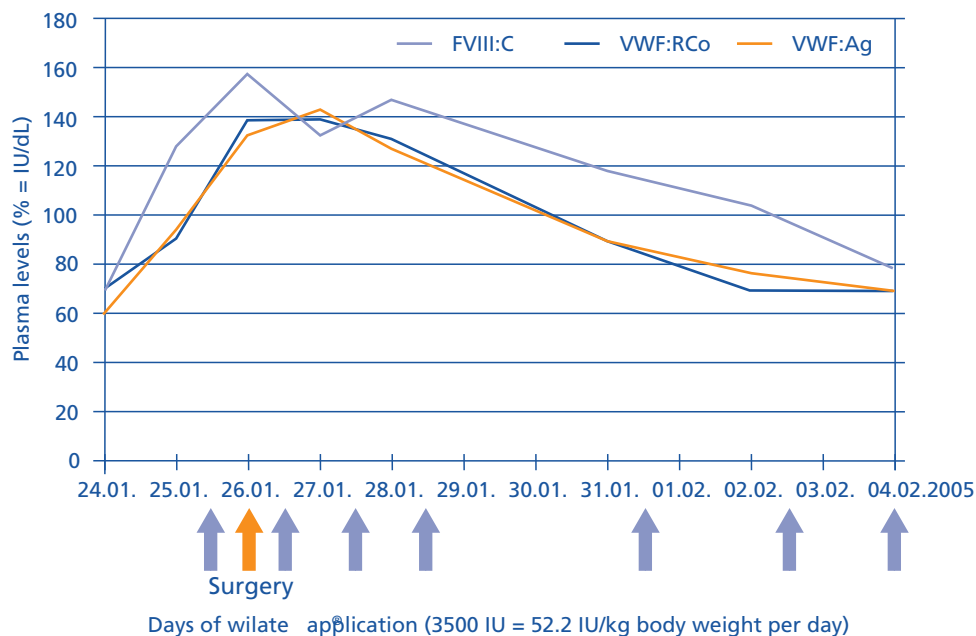


wilate®

**Prospectively Proven
Clinical Efficacy**

Case example 2: wilate® in shoulder surgery in a VWD type 1 patient²³

As in the examples of a shoulder surgery in a type 1 VWD patient, and total knee replacement in a type 3 patient, wilate®'s physiological 1:1 VWF:RCo/FVIII:C ratio may help in the avoidance of potentially very high FVIII:C levels after repeated dosing in surgical patients thus reducing the thrombotic risk.

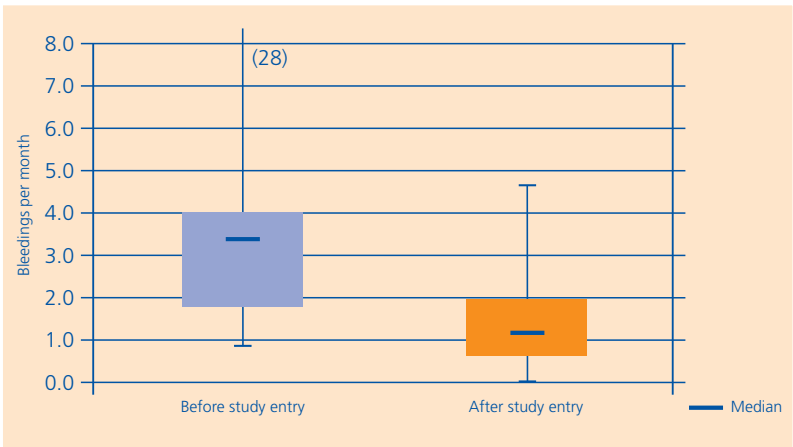


wilate® is Successful in Prophylaxis⁷

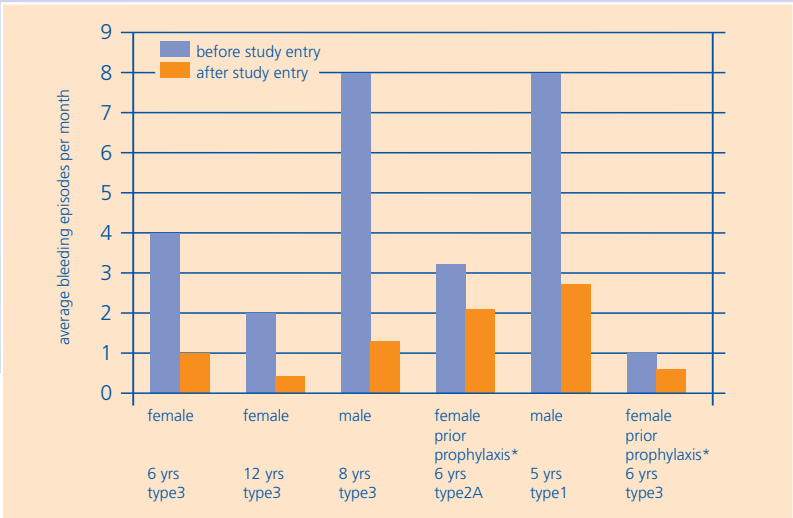
wilate® successfully reduces frequency of bleeding episodes⁷

19 patients received prophylactic treatment for an average period of 14.8 months (range 3–46). The bleeding frequency was clearly reduced under wilate® therapy. The mean frequency before wilate® prophylaxis was 5 bleeds/ month, and was reduced to a frequency of 1 bleed per month after start of wilate® treatment.

The reduction of bleeding frequency in 19 patients after start of wilate® prophylaxis (p=0.0028, Wilcoxon)⁷



The reduction of bleeding frequency in children of 12 years or less⁷



Two of the children, marked with an asterisk, were on a prior prophylaxis with an older generation VWF/FVIII concentrate, at the same FVIII dosing.

wilate® is Convenient to Dose and Administer

Simple dosage calculation

The balanced content of active substances (VWF:RCo and FVIII:C) facilitates simple dosage calculation in VWD therapy, based on the declared units (vial sizes of 450 IU or 900 IU). Thus, differentiation according to FVIII:C or VWF:RCo is not necessarily required. In accordance with the dosage instructions for wilate®, a dose of 20–50 IU/kg body weight is normally recommended for haemorrhages in VWD.*

wilate® standard dosage for treating of bleeding episodes in VWD

20–50 IU/kg body weight every 12–24 hours

* Prescribing information, wilate® 450/900, version November 2008

Rapidly dissolved and administered

wilate® is rapidly dissolved in a small injection volume (450 IU in 5 ml, 900 IU in 10 ml). This means quicker and simpler handling, for doctors, nurses and patients.

For home treatment, during travel and in the clinical routine, wilate® offers additional advantage. Its shelf life is 36 months in a refrigerator, however, it can be stored up to two months also at room temperature, after which it has to be used.

The reconstituted solution is stable up to 12 hours at room temperature (max. 25°C).

wilate®

Convenient for
Dosing and
Administration

Naturally Balanced and Coordinated Efficacy for VWD Patients

Basic Information, wilate® 450/900

Indications, storage conditions and other registration details differ from country to country. Please check the local prescribing information.

Human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF)

Composition: The medicinal products contain per vial 450 IU/900 IU human coagulation factor VIII (FVIII) and 400 IU/800 IU human von Willebrand factor (VWF) prepared from human plasma for fractionation. Solvent: Water for Injections with 0.1% Polysorbate 80.

Excipients: Sodium chloride, Glycine, Sucrose, Sodium citrate and Calcium chloride, Solvent (Water for injections with 0.1% Polysorbate 80).

Therapeutic Indications: Treatment and prophylaxis of bleeding episodes, and bleeding in minor and major surgery in patients with von Willebrand disease (VWD) and haemophilia A (congenital or acquired FVIII deficiency).

Contra-Indications: Hypersensitivity to the active substances or to any of the excipients.

Undesirable effects: In rare occasions: fever, hypersensitivity or allergic reactions, in some cases progress to severe anaphylaxis (including shock).

Von Willebrand disease: Patients with VWD, especially type 3 patients, may very rarely develop neutralising antibodies to VWF. There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors.

Haemophilia A: Patients may rarely develop neutralising antibodies (inhibitors) to FVIII.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Shelf-life/Storage: 36 months at +2°C to +8°C. The concentrate can be stored for up to two months at room temperature (max. 25°C) after which it should be immediately used.

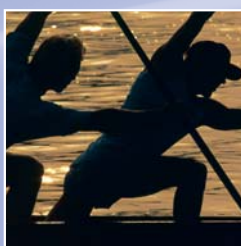
On prescription only

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Version: June 2009

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Developed to Set New Standards in VWD Treatment

wilate® at a glance

- Double virus inactivated
- VWF quality close to normal plasma
- High purity for excellent tolerability
- VWF and FVIII in a physiological ratio of 1 to 1
- Excellent clinical efficacy and tolerability
- Rapidly dissolved in a small volume

wilate®

**New Generation
VWF/FVIII
Concentrate**

Octapharma AG
Seidenstraße 2
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www.octapharma.com

Date of preparation: June 2009

octapharma

For the safe and optimal use of human proteins