

PRODUCT MONOGRAPH

wilate[®]

Human Coagulation Factor VIII (FVIII) and human von Willebrand factor (VWF)

Powder and solvent for solution for injection

450 IU FVIII and 400 IU VWF reconstituted with 5 mL of diluent
900 IU FVIII and 800 IU VWF reconstituted with 10 mL of diluent

ATC code: B02BD06 D68.0

Manufactured by:

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wilate® 450/900

Human coagulation factor VIII and human von Willebrand factor

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Injection	Powder and solvent for solution for injection/ 450 IU/900 IU FVIII and 400 IU/800 IU VWF per vial	Sodium chloride, Glycine, Sucrose, Sodium citrate and Calcium chloride, Solvent (Water for injection with 0.1% Polysorbate 80) <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

DESCRIPTION

wilate® is a plasma-derived, stable, highly purified concentrate of freeze-dried active human coagulation factor VIII (FVIII) and von Willebrand factor (VWF). It is prepared from cryoprecipitate. wilate® is supplied as a powder for reconstitution and intravenous injection.

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: 5 ml/10 ml Water for Injections with 0.1% Polysorbate 80

The reconstituted solution, which is prepared with the enclosed solvent, contains 90 IU/ml FVIII and 80 IU/ml VWF.

The potency of FVIII (FVIII:C) is determined by using the current “International Standard for Human Coagulation Factor VIII Concentrate”. The determination of the VWF potency is carried out by determination of the Ristocetin Cofactor potency (VWF:RCo) by using the current “International standard for von Willebrand Factor Concentrate”. The determinations are carried out according to European Pharmacopoeia (Ph.Eur.).

The specific activity of wilate[®] is ≥ 60 IU FVIII:C/mg and ≥ 53 IU VWF:RCo/mg of total protein.

This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases. Two effective virus inactivation steps provide a significant assurance in terms of viral safety. These are a solvent/detergent (S/D) virus inactivation step and a dry heat treatment in the final container at +100 °C for 120 minutes. The efficacy of these two viral inactivation steps has been validated in accordance with international guidelines. (Refer to WARNINGS AND PRECAUTIONS section).

For list of excipients, see above table.

INDICATIONS AND CLINICAL USE

wilate[®] is indicated for:

Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital or acquired FVIII deficiency) and for the prevention and treatment of bleeding in minor surgical procedures.

Clinical trials to evaluate the safety and efficacy of wilate[®] in major surgeries are ongoing. Therefore, limited data are presently available on which to evaluate or to base dosing recommendations. Thus, in the case of major surgical interventions, a precise monitoring of the substitution therapy by means of coagulation analysis (FVIII:C) is indispensable.

Geriatrics (> 65 years of age):

Although some of the patients who participated in the wilate[®] studies were > 65 years of age, no appropriate subgroup analyses were performed and therefore no data regarding use of wilate[®] in the geriatric population are available at this point.

Pediatrics (< 12 years of age):

There are insufficient data to recommend the use of wilate[®] in children below 12 years of age and in previously untreated hemophilia A patients.

Studies are being conducted in children with severe hemophilia A and VWD.

CONTRAINDICATIONS

wilate[®] is contraindicated for patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering to the patient (see Warnings – General).

General

Products made from human plasma may contain infectious agents such as viruses that can cause disease. 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. Like other plasma products, wilate[®] carries the possibility for transmission of blood-borne viral agents, and theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent.

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 are of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. hemolytic anemia). Eight patients in clinical studies were found to have seroconverted to parvovirus B19 antibody positive. In some cases the implicated lots of wilate[®] were found to be parvovirus B19 positive (PCR).

The plasma used for wilate[®] will be US-source plasma from FDA licensed donation centres, which is routinely tested for parvovirus B19 by PCR in minipools.

It is strongly recommended that every time that wilate[®] is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived FVIII/VWF concentrates.

Immune

The formation of neutralizing antibodies (inhibitors) to FVIII is a known complication in the management of individuals with hemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Modified Bethesda Units (BU) per mL of plasma using the modified assay. The risk of

developing inhibitors is correlated to the exposure to anti-hemophilic FVIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Patients treated with FVIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory test. If such inhibitors occur, the condition will manifest as an insufficient clinical response. Management of such patients should be directed by physicians with experience in the care of patients with haemostatic disorders.

In previously untreated patients the inhibitor rate is estimated to be about <25%. Data, on which the rate is based, is from an on-going clinical study, therefore final results may differ.

In previously treated patients there is insufficient data to estimate the rate of inhibitor development in patients commencing treatment with wilate[®]. Published data, based on treatment with other factor VIII products estimate the rate of inhibitor development to be in the range of 2 to 3% [12, 13]. Data from on-going and future studies with wilate[®] and from post-marketing reviews will provide more accurate information on the rate of inhibitor development associated with the transfer of patients to treatment with wilate[®].

(See also ADVERSE REACTIONS).

Peri-Operative Considerations

See DOSAGE AND ADMINISTRATION for instructions for prevention of bleeding in case of surgery or severe trauma.

Sensitivity/Resistance

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician. If patients develop inhibitors to FVIII, the condition will manifest itself as an inadequate clinical response. Such antibodies may precipitate and may occur concomitantly to anaphylactic reactions. Therefore, patients experiencing an anaphylactic reaction should be evaluated for the presence of inhibitors.

In case of shock, the current medical standards for treatment of shock are to be observed.

Skin

See Sensitivity/Resistance above.

Special Populations

Pregnant Women:

Animal reproduction studies have not been conducted with FVIII/VWF.

Based on the rare occurrence of hemophilia A in women, experience regarding the treatment during pregnancy and breastfeeding is not available. Therefore, wilate[®] should be used during pregnancy and breastfeeding only if clearly indicated.

Nursing Women:

See Pregnant Women above.

Geriatrics (> 65 years of age):

Although some of the patients who participated in the wilate[®] studies were > 65 years of age, no appropriate subgroup analyses were performed and therefore no safety or tolerability data regarding a geriatric population can be presented at this point.

Pediatrics (< 12 years of age):

There are insufficient data to recommend the use of wilate[®] in children below 12 years of age and in previously untreated hemophilia A patients.

Studies are being conducted in children with severe hemophilia A and VWD.

Monitoring and Laboratory Tests

The formation of inhibitors to FVIII in patients with hemophilia A treated with FVIII should be monitored. If the expected FVIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed (Bethesda test) to determine if FVIII inhibitors are present. In patients with high levels of inhibitors, FVIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemostatic disorders.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently, and may in some cases progress to severe anaphylaxis (including shock). In rare occasions, fever has been observed.

Patients with hemophilia A may develop neutralizing antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest as an insufficient clinical response. In such cases, it is recommended that a specialized hemophilia centre be contacted.

In previously untreated patients the inhibitor rate is estimated to be about <25%. Data, on which the rate is based, is from an on-going clinical study, therefore final results may differ.

In previously treated patients there is insufficient data to estimate the rate of inhibitor development in patients commencing treatment with wilate[®]. Published data, based on treatment with other factor VIII products estimate the rate of inhibitor development to be in the range of 2 to 3% [12, 13]. Data from on-going and future studies with wilate[®] and from post-marketing reviews will provide more accurate information on the rate of inhibitor development associated with the transfer of patients to treatment with wilate[®].

Clinical Trial Adverse Drug Reactions

To present as much safety data as available from clinical studies with wilate[®], data from 4 completed studies in hemophilia A and 2 completed studies in VWD are summarized in this section. In total 116 individual patients (68 hemophilia patients and 48 VWD patients) received wilate[®] on about 6,567 occasions (4,142 and 2,425, respectively).

	wilate[®] n= 116 (%)
Immune system disorders	
allergic reactions	0.9
allergic exanthema	0.9
drug induced pruritus	0.9
Psychiatric disorders	
sleep disorder	0.9
Nervous system disorders	
dizziness	1.7
vertigo	0.9
headache	1.7
Respiratory, thoracic and mediastinal disorders	
shortness of breath	0.9
Gastrointestinal disorders	
nausea	0.9
abdominal discomfort	0.9
General disorders & administration site conditions	
fever	1.7

See: Medical Dictionary for Regulatory Activities (MedDRA) Maintenance and Support Services Organization (MSSO), Medical Regulatory Terminology March 2005

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Not applicable.

Abnormal Hematological and Clinical Chemistry Findings

Standard clinical laboratory evaluations were performed in all the studies. There were no particular issues raised for any laboratory parameters in any of the studies.

Post-Market Adverse Drug Reactions

In February 2005, wilate[®] received marketing approval for the treatment of all types of VWD and hemophilia A from the Paul Ehrlich Institute (PEI) in Germany. Since then 3.2 Mio IU of wilate[®] have been sold. Eight patients in clinical studies were found to have seroconverted to parvovirus B19 antibody positive. In some cases the implicated lots of wilate[®] were found to be parvovirus B19 positive (PCR).

The plasma used for wilate[®] will be US-source plasma from FDA licensed donation centres, which is routinely tested for parvovirus B19 by PCR in minipools.

DRUG INTERACTIONS

Overview

No interactions with other medicinal products are known.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

No interactions with other medicinal products are known.

Drug-Laboratory Interactions

There are no particular issues raised for any laboratory parameters in any of the studies.

Drug-Lifestyle Interactions

No effects on ability to drive and use machines have been observed.

DOSAGE AND ADMINISTRATION

Dosing Considerations

After 24-48 hours of treatment, in order to avoid an excessive rise in FVIII:C, reduced doses and/or prolongation of the dose interval should be considered.

Recommended Dose and Dosage Adjustment

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

The number of units of FVIII administered is expressed in International Units (IU), which are related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed

either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for FVIII in plasma).

The dosage and duration of the substitution therapy depend on the severity of the FVIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

One IU of FVIII activity is equivalent to that quantity of FVIII in one ml of normal human plasma.

The calculation of the required dosage of FVIII is based on the empirical finding that 1 IU FVIII:C/kg BW raises the plasma level by 1.5-2% of normal activity. The required dosage is determined using the following formula:

$$\text{Required IU} = \text{BW (kg)} \times \text{desired FVIII rise (\%)} \times 0.5 \text{ IU/kg}$$

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. The following table can be used to guide dosing in bleeding episodes and surgery in adult patients and children older than 6 years.

In the case of the following hemorrhagic events, the FVIII:C should not fall below the given plasma level in the corresponding period.

Table 1: Hemophilia A - Treatment Scheme for Hemorrhages and Surgery

Degree of hemorrhage/ Type of surgical procedure	FVIII level required (%) (IU/dl)	Frequency of Doses (hours)/Duration of Therapy (days)
Hemorrhage		
Mild hemorrhage: Early hemarthrosis, muscle bleed, nosebleed, oral bleed and other minor injuries	20 – 40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleed or hematoma	30 – 60	Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and disability are resolved.
Life threatening hemorrhage: cerebral hemorrhage, blunt trauma without visible bleeding site, severe abdominal bleed resp. internal bleeding, throat bleed	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
<i>Minor</i> including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
<i>Major</i>	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FVIII activity of 30% to 60%.

During the course of treatment, appropriate determination of FVIII:C levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (FVIII:C) is indispensable. Individual patients may vary in their response to FVIII treatment, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

Prophylaxis:

For long-term prophylaxis against bleedings in patients with severe hemophilia A, doses of about 20 IU wilate[®]/kg BW should be given at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

There are insufficient data to recommend the use of wilate[®] in children below 12 years of age and in previously untreated haemophilia A patients.

Studies are being conducted in children with severe hemophilia A and VWD.

Missed Dose

If a patient on prophylactic treatment missed a dose, the missed dose should be taken as soon as possible, and then treatment should continue as before. If a dose is skipped, the next dose must usually not be doubled.

In the unlikely event that a patient who is actively bleeding is missing a dose, it may be appropriate to adopt the next dosage depending on the extent of the bleeding and on the patient's clinical condition.

Administration

wilate[®] is administered via intravenous infusion.

Instructions for Reconstitution:

1. Warm the wilate[®] powder and solvent in the closed vials up to room temperature (maximum 37°C). This temperature should be maintained during reconstitution.
2. Remove the flip caps from the wilate[®] vial and the solvent vial and clean the rubber stoppers with an alcohol swab.
3. Peel away the lid of the outer package of the Mix2Vial[™] transfer set. Place the solvent vial on an even surface and hold the vial firmly. Take the Mix2Vial[™] together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial[™] firmly through the rubber stopper of the solvent vial. While holding onto the solvent vial, carefully remove the outer package from the Mix2Vial[™], being careful to leave the Mix2Vial[™] attached firmly to the solvent vial.

4. With the wilate[®] vial held firmly on an even surface, quickly invert the solvent vial (with the Mix2Vial[™] attached) and push the transparent plastic cannula end of the Mix2Vial[™] firmly through the stopper of the wilate[®] vial. The solvent will be drawn into the wilate[®] vial by vacuum.
5. With both vials still attached, slowly rotate the wilate[®] vial to ensure the product is fully dissolved, giving a clear or slightly opalescent, colourless or slightly yellow solution. Once the contents of the wilate[®] vial are dissolved, firmly hold both the transparent and blue parts of the Mix2Vial[™]. Unscrew the Mix2Vial[™] into two separate pieces with the vials still attached and discard the empty solvent vial and the blue part of the Mix2Vial[™].

Instructions for injection:

As a precautionary measure, the patients pulse rate should be measured before and during the injection. If a marked increase in the pulse rate occurs the injection speed must be reduced or the administration must be interrupted.

1. Attach a plastic sterile disposable syringe to the transparent part of Mix2Vial[™]. Invert the system and draw the reconstituted wilate[®] into the syringe.
2. Once the wilate[®] solution has been transferred into the syringe, firmly hold the barrel of the syringe (keeping it facing down) and detach the Mix2Vial[™] from the syringe. Discard the Mix2Vial[™] (transparent plastic part) and the empty wilate[®] vial.
3. Clean the intended injection site with an alcohol swab.
4. Attach a suitable infusion needle to the syringe.
5. Inject the solution intravenously at a slow speed of 2-3 mL/minute.

Incompatibilities

wilate[®] must not be mixed with other medicinal products or administered simultaneously with other intravenous preparation in the same infusion set.

Shelf-life

wilate[®] has a shelf-life of 3 years. The powder should be reconstituted only directly before injection. After reconstitution the solution should be used immediately.

Special Precautions for Storage

wilate[®] and solvent can be stored at between +2°C and +8°C until the indicated expiry date. Within this period wilate[®] and solvent may be stored for a single block of up to 6 months at room

temperature (max. +25°C). If stored at room temperature (max. +25°C) wilate[®] must either be used within 6 months or discarded. Protect from light.

Do not freeze. The reconstituted solution should be used on one occasion only. Any solution remaining should be discarded.

OVERDOSAGE

No symptoms of overdose with human FVIII or VWF have been reported.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

VWF is a multimeric protein with two key functions. It is an adhesive molecule, which mediates the binding between platelets and damaged sub-endothelial tissues. It is also a carrier protein, involved in the transport and stabilization of FVIII. Patients suffering from VWD have a deficiency or abnormality of VWF. A reduction in VWF concentration in the bloodstream results in low FVIII activity and abnormal platelet function, as the platelets are prevented from adhering to sub-endothelial tissue. As a result, excessive bleeding will occur.

In human plasma, the FVIII/VWF circulates as protein complex consisting of a small molecule with coagulant activity (FVIII), which is non-covalently bound to a larger carrier protein (VWF). FVIII is involved in the intrinsic pathway of blood coagulation, functioning as the co-factor for the factor IXa-mediated activation of factor X. Patients with hemophilia A are deficient in factor VIII, and are therefore predisposed to episodes of recurrent bleeding.

The coagulation factors FVIII and VWF in wilate[®] are normal constituents of human plasma and act like the endogenous FVIII and VWF. Therefore, wilate[®] is a suitable treatment option for the prophylaxis and treatment of bleeding episodes in patients with hemophilia A.

Pharmacodynamics

Pharmacotherapeutic group: Von Willebrand factor and coagulation factor VIII in combination.

The FVIII/VWF complex consists of two molecules (FVIII and VWF) with different physiological functions. When infused into a hemophilia patient, FVIII binds to VWF in the patient's circulation. Activated FVIII (FVIIIa) acts as a cofactor for activated factor IX (FIXa), accelerating the conversion of factor X to activated factor X (FXa). FXa converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

Hemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of FVIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma

levels of FVIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

In addition to its role as a FVIII-protecting protein, VWF mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

Pharmacokinetics

FVIII (from the concentrate) is a normal constituent of the human plasma and acts like the endogenous FVIII. After injection of the product, approximately two thirds to three quarters of the FVIII remain in the circulation. The level of FVIII:C reached in the plasma should be between 80-120% of the predicted FVIII:C.

FVIII:C decreases by a two-phase exponential decay. In the initial phase, distribution between the intravascular and other compartments (body fluids) occurs with a half-life of elimination from the plasma of 3 to 6 hours. In the subsequent slower phase, the half-life varies between 8 to 18 hours, with an average of 15 hours. This corresponds to the true biological half-life.

The following results were observed in one clinical study in 12 patients (one-stage clotting assay, single measurement):

Table 2: Pharmacokinetics of wilate[®] (FVIII:C) in Hemophilia A Patients

Parameter	Mean	SD
Recovery %/IU/kg	2.04	1.15
AUC _{norm} % * h/IU/kg	37.8	10.0
Half-life (h)	14.8	3.1
MRT (h)	20.4	4.5
Clearance mL/h/kg	2.9	1.0

Key: AUC = area under the curve; MRT = mean residence time; SD = standard deviation

STORAGE AND STABILITY

wilate[®] and solvent can be stored at between +2°C and +8°C until the indicated expiry date. Within this period wilate[®] and solvent may be stored for a single block of up to 6 months at room temperature (max. +25°C). If stored at room temperature (max. +25°C) wilate[®] must either be used within 6 months or discarded. Protect from light.

Do not freeze. The reconstituted solution should be used on one occasion only. Any solution remaining should be discarded.

SPECIAL HANDLING INSTRUCTIONS

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Nature and contents of container

Powder and solvent for solution for injection.

Package sizes:

wilate[®] 450 in 5 mL

1 package contains:

1 vial with powder

1 vial with solvent (5 ml Water for Injections with 0.1% Polysorbate 80)

Mix2Vial[™] transfer set with integrated filter.

wilate[®] 900 in 10 mL

1 package contains:

1 vial with powder

1 vial with solvent (10 ml Water for Injections with 0.1% Polysorbate 80)

Mix2Vial[™] transfer set with integrated filter.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	wilate [®] 450/900
Chemical name:	Human coagulation factor VIII and human von Willebrand factor
Molecular formula and molecular mass:	not applicable
Structural formula:	not applicable

Physicochemical properties:

Table 3: Purity and Activity of wilate[®]

Analysis	Units	wilate [®] (mean, range)
Total protein	mg/mL	0.8 (0.5-1.0)
Specific Activity	IU FVIII:C* / mg total protein	120 (91-204)
Fibronectin	mg/mL	< 0.05
Fibrinogen	mg/mL	< 0.13
FVIII:C*	IU/mL	nominal 90
VWF:Rco**	IU/mL	nominal 80
Ratio between two parameters	IU/IU	0.9

* 7th International Standard pp/678 (NIBSC)

** 1st International Standard 00/514

Product Characteristics

wilate[®] is manufactured by a novel production process using new biotechnological methods and newly developed chromatographic media. This process makes it possible to manufacture FVIII/VWF complex in its native form and to reduce the high levels of accompanying plasma proteins that can be found in other VWF-containing FVIII preparations.

It is prepared from cryoprecipitate. Two effective virus inactivation steps provide a significant assurance in terms of viral safety, i.e. a S/D virus inactivation step and a dry heat treatment in the final container at +100 °C for 120 minutes.

The high purity of the compound is demonstrated by different high resolution analytical methods including size exclusion high pressure liquid chromatography (SE-PLC), SDS-PAGE, immunoblotting, and agarose gel electrophoresis.

wilate[®] is a plasma-derived, stable, highly purified freeze-dried human coagulation FVIII/VWF preparation. As the FVIII is complexed with its native stabilizer VWF, no additional stabilizing proteins are added during production.

Viral Inactivation

The plasma used for the manufacture of wilate[®] is obtained from FDA approved plasma donation centers according to 21 CFR 640.30 "PLASMA" and 21 CFR 640.60 "SOURCE PLASMA".

Double Virus Inactivation During the Manufacturing Process

Two well-established process steps are incorporated: S/D and terminal dry heat treatment in the final container at +100°C for 120 minutes.

The viral safety is mainly based on the solvent/detergent (S/D) treatment and the terminal dry-heat treatment (TDH) step. In addition, the ion-exchange chromatography step was also investigated for its capacity to remove viruses. Chromatographic steps are known to contribute to the removal of potential viral contaminants, as discussed by the CPMP in the "Note for Guidance on Plasma derived Medicinal Products" (CPMP/BWP/269/95).

The **S/D method**: the efficacy is demonstrated at $> 7.52 \log_{10}$ inactivation for HIV, $\geq 8.54 \log_{10}$ inactivation for PRV, $\geq 4.18 \log_{10}$ inactivation for BVDV, and $\geq 8.63 \log_{10}$ inactivation for Sindbis virus. No infectivity was found after 1-2 minutes of S/D treatment in these validation studies.

The **Ion-exchange chromatography** step led to a reduction factor of $3.29 \log_{10}$ for PPV and $1.16 - 1.93 \log_{10}$ for HAV.

Dry heat treatment: HAV infectivity was already below the limit of detection after 30 minutes of dry heat treatment. The reduction factor was $\geq 5.69 \log_{10}$ steps achieved after 120 minutes of heating. Dry heat treatment of PPV led to a reduction factor of about $1-2 \log_{10}$ after 30 minutes and about $2.57-4.12 \log_{10}$ after 120 minutes of heating. Based on these results for two highly resistant non-enveloped viruses, dry heat treatment in the final container is performed at +100 °C for 120 minutes.

The results of virus validation studies document a mean cumulative total process reduction capacity of > 12.43 to $> 13.31 \log_{10}$ for HIV-1, > 12.53 to $> 13.41 \log_{10}$ for PRV, $> 4.18 \log_{10}$ for BVDV, > 14.14 to $> 15.14 \log_{10}$ for Sindbis virus, > 6.85 to $> 7.62 \log_{10}$ for HAV, and $5.86 - 7.41 \log_{10}$ for PPV.

CLINICAL TRIALS

Study demographics and trial design

Four clinical studies (TMAE-101, TMAE-102, TMAE-108, TMAE-110) have been completed with wilate[®] in previously treated, severe hemophilia A patients.

Table 4: Summary of Patient Demographics for Clinical Trials in Hemophilia A

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N = patients in study), (n = new individuals)	Mean age (Range)	Gender
TMAE-101	Open label, non-randomized, non-controlled, Phase II trial	3 single doses (40 IU/kg body weight), given IV at baseline, 3 and 6 months. wilate [®] also available according to needs of patients during study Study duration: 6 months	Severe hemophilia A PTPs (N=12; n=12) 2 patients were enrolled for peri-operative treatment only N=14	33 years (18-56)	M
TMAE-102	Open label, non-randomized, non-controlled, Phase II trial	3 single doses (40 IU/kg BW) given IV at baseline, 3 and 6 months, or adapted to needs of patients. wilate [®] also available according to needs of patients during study Study duration: 6 months	Severe hemophilia A PTPs (N=20; n=20) 4 patients were recruited for treatment during surgery only. N=24	24 (11-59)	M
TMAE-108	Open label, non-randomized, non-controlled, Phase II trial	3 single doses (40 IU/kg body weight), given IV at baseline, 3 and 6 months. wilate [®] also available according to needs of patients during study Study duration: 6 months	Severe hemophilia A PTPs (N=20; n=1)	25 (11-59)	M
TMAE-110	Open label, non-randomized, non-controlled, Phase III trial	3 single doses (40 IU/kg body weight), given IV at baseline, 3 and 6 months. wilate [®] also available according to needs of patients during study Study duration: 6 months	Severe hemophilia A PTPs (N=35; n=35)	31 (12-66)	M

The studies were designed to evaluate the efficacy and safety of wilate[®] in PTPs with severe hemophilia A. Study TMAE-101 also investigated the PK profile. In all studies recovery was calculated, and results presented, according to two definitions:

- Definition 1 indicated incremental recovery, defined as the rise in plasma FVIII (%) achieved with 1 IU wilate[®]/kg BW.
- Definition 2 indicated the absolute recovery, defined as the rise in plasma FVIII (%) achieved by a dose of approximately 40 IU wilate[®]/kg BW.

Study results

Study TMAE-101

12 previously treated patients (>150 previous exposure days) with severe hemophilia A (FVIII:C < 1%), were treated with wilate[®]. Two patients were enrolled for peri-operative treatment only. One of the 12 patients was additionally treated during a surgical intervention.

An overview of the FVIII consumption is provided in the table below.

Table 5: Study TMAE-101 (n=12): FVIII Consumption per Month, Year, and Event

FVIII Consumption	n	Mean ± SD
Mean dose / kg / month	12	152.8 ± 65.1 IU/kg
Mean dose / kg / year	12	1,833 ± 780 IU/kg
Mean dose / kg / event: prophylactic exposure day *	9	29.2 ± 9.5 IU/kg
Mean dose / kg / event: prophylactic exposure day **	12	34.2 ± 9.8 IU/kg
Mean dose / kg / event: bleeding episode ***	12	33.7 ± 12.7 IU/kg

* without study related treatments ** including study related treatments

*** without surgeries.

- FVIII Recovery Results

Table 6: Results of Study TMAE-101 in Hemophilia A (n=12): FVIII Recovery Results

Parameter	Unit	Baseline	3-month visit	6-month visit
One-stage assay		Geometric Means \pm SD (range)		
Recovery (def. 1)	%/IU/kg	2.04 / 1.15 (1.72 – 2.49)	2.02 / 1.26 (1.32 – 3.11)	2.07 / 1.20 (1.51 – 2.87)
Recovery (def. 2)	%	81.8 / 1.15 (61.5 – 102)	83.8 / 1.24 (59.2 – 123)	82.0 / 1.19 (60.3 – 117)
Chromogenic Assay		Geometric Means \pm SD (range)		
Recovery (def. 1)	%/IU/kg	2.27/1.20 (1.75-3.10)	2.31/1.20 (1.60-3.17)	2.26/1.19 (1.74-2.92)
Recovery (def. 2)	%	91.1/1.21 (66.9-124)	94.4/1.19 (71.7-133)	89.6/1.18 (70.6-114)

Recovery def. 1 (incremental recovery); recovery def. 2 (absolute recovery)

The analysis of recovery was based on FVIII concentrations determined after administration of wilate[®] with both a one-stage and a chromogenic assay. The results were similar at each visit and for both FVIII assays applied.

From these results obtained with both assays, no statistically significant differences were observed in the recovery over time. Likewise, no statistically significant differences were observed in the maximum concentrations of FVIII, which remained constant over time. The recovery results were additionally submitted to an analysis of variance (ANOVA) of the log-transformed values. No statistically significant time effect for either incremental recovery (def. 1) or absolute recovery (def. 2) was observed for the one-stage assay (p=0.822 and p=0.768, respectively) or for the chromogenic (p=0.764 and p=0.302, respectively).

The results indicated good efficacy with wilate[®]. The incremental recovery (def. 1) calculated from the results of both assays are consistently higher than 2, indicating that 1 IU of wilate[®]/kg BW will raise FVIII:C by more than 2%. A recovery of 2 %/IU/kg is in the upper range of what is known for other FVIII concentrates and should provide a good efficacy when treating bleeding episodes. Similarly, the absolute recovery (def. 2) was shown to be higher than 80% after a single, intravenous dose of approximately 40 IU wilate[®]/kg BW.

- Treatment of Bleeding Episodes

A total of 192 bleeding episodes were recorded during this study. Three patients were mainly treated prophylactically. On average, a dose of 27.0 IU wilate[®]/kg was administered on each day of a bleeding episode. This is in the range of general recommendations for treatment of bleeding episodes. The average duration of bleeding episode therapy was 1.3 days.

Table 7: Results of Study TMAE-101 in Hemophilia A (n=12): Treatment of Bleeding Episodes (n=192)

	Mean \pm SD	Minimum	Maximum
No. of bleeding episodes / patient	16.0 \pm 9.7	1	32
No. of days of treatment / patient	20.1 \pm 12.9	1.0	39.0
No. of treatment days / bleeding episode / patient	1.3 \pm 0.3	1.0	2.0
Consumption of FVIII (IU)/patient	35,958 \pm 28,371	2,000	106,500
Dose / exposure day (IU)	1814 \pm 512	1027	2803
Dose / exposure day per kg BW (IU)	27.0 \pm 7.2	15.6	37.7

In terms of efficacy assessments, 88.0% of bleeding episodes were assessed as ‘excellent’ or ‘good’. In all cases, the episodes could be controlled with wilate[®] and all affected patients remained in the study.

- Treatment During Surgical Intervention

Evaluation of continuous infusion with wilate[®] during surgical interventions was limited to 3 cases. In 2 cases efficacy was assessed as ‘good’, and in 1 case as ‘excellent’.

Study TMAE-102

20 previously treated patients (>150 previous exposure days), with severe hemophilia A (FVIII:C < 1%), were treated with wilate[®]. The duration of the study was 6 months for patients in the treatment part. In addition to the 20 patients, who participated in the treatment part of the study (including 3 surgical procedures) there were 4 patients recruited for treatment during surgery only.

Table 8: Study TMAE-102 (n=20): FVIII Consumption per Month, Year, and Event

FVIII Consumption	n	Mean \pm SD
Mean dose / kg / month	20	163.0 \pm 63.6 IU/kg
Mean dose / kg / year	20	1,956 \pm 763 IU/kg
Mean dose / kg / event: prophylactic exposure day *	14	20.8 \pm 6.8 IU/kg
Mean dose / kg / event: prophylactic exposure day **	20	31.2 \pm 11.3 IU/kg
Mean dose / kg / event: bleeding episode ***	20	32.4 \pm 8.8 IU/kg

* without study related treatments ** including study related treatments

*** without surgeries

- FVIII Recovery Results

The following Table compares FVIII recovery results using labeled and actual potency, measured by chromogenic assay. The batches administered gave very similar results for all 3 recovery assessments.

Table 9 Study TMAE-102 (n=20): FVIII Recovery Results (Def. 1) - Labeled vs. Actual Potency – Chromogenic Assay

	Arithmetic Mean		SD		Median	
	Labeled	Actual	Labeled	Actual	Labeled	Actual
Baseline	1.75	1.70	0.19	0.18	1.74	1.67
3-months	1.65	1.67	0.22	0.19	1.64	1.66
6-months	1.59	1.78	0.23	0.29	1.60	1.84

- Treatment of Bleeding Episodes

A total of 338 bleeding episodes, including peri-operative treatments, were recorded during the study. Five patients were mainly treated prophylactically.

An average dose of 26.9 IU wilate[®]/kg was administered on each day of a bleeding episode. This is in the range of general recommendations for treatment of bleeding episodes. The average duration of bleeding episode therapy was 1.3 days.

Table 10: Study TMAE-102 (n=20 Patients): Treatment of Bleeding Episodes (n=338)

	Mean + SD	Minimum	Maximum
No. of bleeding episodes / patient	16.9 ± 8.8	1.0	37.0
No. of exposure days / patient	22.1 ± 12.4	1.0	48.0
No. of treatment days / bleeding episode/ patient	1.3 ± 0.3	1.0	1.9
Consumption of FVIII (IU) / patient	34,400 ± 24,045	1,500	112,000
Dose / exposure day (IU)	1,579 ± 682	886	3,500
Dose / exposure day per kg BW (IU)	26.9 ± 7.41	15.9	46.9

In terms of efficacy assessments, 99.1 % of the bleeding episodes were assessed as ‘good’ (11.8 %) or ‘excellent’ (87.3 %). In all cases, the episodes could be controlled with wilate[®] and all affected patients remained in the study.

- Treatment During Surgical Intervention

For the evaluation of wilate[®] during surgical interventions 7 cases were available. In all cases efficacy was assessed as ‘excellent’. On 3 peri-operative occasions, wilate[®] was given as a continuous infusion. Again, the efficacy was considered to be ‘excellent’.

Study TMAE-108

20 previously treated patients (19 participated in previous Study TMAE-102) were treated with wilate[®], which could be also given on demand or prophylactically according to the clinical needs of the patients and the recommendations of the treating physician.

An overview of the FVIII consumption is provided in the table below.

Table 11: Study TMAE-108 (n=20): FVIII Consumption per Month, Year, and Event

FVIII Consumption	n	Mean ± SD
Mean dose / kg / month	20	190.4 ± 46.5 IU/kg
Mean dose / kg / year	20	2,285 ± 558 IU/kg
Mean dose / kg / event: prophylactic exposure day *	19	23.2 ± 7.0 IU/kg
Mean dose / kg / event: prophylactic exposure day **	20	28.6 ± 8.1 IU/kg
Mean dose / kg / event: bleeding episode ***	16	34.0 ± 13.6 IU/kg

* without study related treatments ** including study related treatments

*** without surgeries.

An overview of the incremental recovery based on the measured potency of the drug is presented in Table 12.

Table 12: Study TMAE-108 (n=20): FVIII Recovery Results (Def. 1) Labeled vs. Actual Potency – Chromogenic Assay

	Arithmetic Mean		Standard Deviation		Median	
	Labeled	Actual	Labeled	Actual	Labeled	Actual
Baseline	2.07	1.84	0.44	0.47	1.98	1.73
3-months	1.91	1.69	0.29	0.29	1.86	1.60
6-months	1.83	1.74	0.30	0.31	1.80	1.68

- **Treatment of Bleeding Episodes**

A total of 302 bleeding episodes were recorded during the study for 16 out of the 20 enrolled patients. On average, a daily dose of 26.53 IU wilate[®]/kg BW was administered to stop bleeding. This is in the range of general recommendations for treatment of bleeding episodes. The average duration of bleeding episode therapy was 1.27 days.

Table 13: Study TMAE-108 (n=16 Patients)*: Treatment of Bleeding Episodes (n=302)

	Mean ± SD	Minimum	Maximum
Total no. of bleeding episodes/patient	18.88 ± 11.83	5.00	37.00
Total no. of days of treatment/patient	23.63 ± 15.25	5.00	53.00
Average no. of treatment days/ bleeding episode/patient	1.27 ± 0.36	1.00	2.17
Total consumption of FVIII (IU)/patient	35,656.25 ± 26,931.84	9,000.00	100,000.00
Average dose/exposure day (IU)	1,626.30 ± 679.20	882.35	2,740.74
Average dose/exposure day/ kg body weight (IU)	26.53 ± 6.07	18.97	35.72

* n=16 (4 patients had been treated prophylactically with wilate[®] throughout the study, and did not experience any bleeding episodes).

For none of the 302 bleeding episodes treated, was an assessment of efficacy given as ‘none’ or ‘moderate’. The overwhelming majority were assessed as ‘excellent’ (98.68%), with the remainder rated ‘good’ (1.32 %). In all cases, the bleeding episodes were stopped with wilate[®] treatment.

Patients could also be treated prophylactically with wilate[®]. On average the patients received 23 IU/kg BW/exposure day. This average dose is considered to be well within the range of an adequately efficacious FVIII product. During the study period the patients needed on average 1.82 exposure days to wilate[®]/week.

15 patients had prophylactic treatment periods with wilate[®] with a duration of at least 4 weeks. In this subpopulation, the total number of prophylactic exposure days was 587. All patients had a baseline FVIII concentration of < 1%, i.e. were severe haemophiliacs. A total of 575 (98%) prophylactic wilate[®] doses can be regarded as successful, i.e. no haemorrhage occurred within 2 days after the administration. It is worth to be mentioned that in all patients (n=12) who had a PT period of > 8 weeks in sequence, the success rate was above 90%, in 8 patients with a PT period of > 8 weeks, the success rate was even 100%.

The efficacy results indicated that wilate[®], given as an IV dose, is a valuable, new alternative to achieve an incremental recovery of FVIII in the range of 1.5-2.0%/IU wilate[®]/kg BW. The efficacy of wilate[®] for prophylactic treatment and the treatment of bleeding episodes was also convincingly shown.

Study TMAE-110

35 previously treated patients, with severe hemophilia A, were treated with wilate[®]. The dosing frequency and the actual dose for treating spontaneous bleedings or for prophylactic treatment depended on the clinical situation of the patient, e.g. the severity of the bleeding.

The following table summarizes the relevant results for FVIII obtained using the actual potency of wilate[®].

Table 14: Study TMAE-110 (n=35): FVIII Recovery Results Actual Potency

Parameter (%IU/kg)	Baseline Geometric Means \pm SD (Range)	3-Month Visit Geometric Means \pm SD (Range)	6-Month Visit Geometric Means \pm SD (Range)
One-stage assay			
C _{max norm}	1.90 \pm 1.24 (1.21-3.07)	1.96 \pm 1.22 (1.32-3.01)	1.95 \pm 1.24 (1.23-2.95)
Recovery (def. 1)	1.89 \pm 1.24 (1.21-3.04)	1.93 \pm 1.22 (1.32-2.96)	1.92 \pm 1.23 (1.23-2.79)
Chromogenic			
C _{max norm}	1.97 \pm 1.22 (1.40-3.02)	2.03 \pm 1.25 (1.37-3.05)	1.91 \pm 1.22 (1.34-2.80)
Recovery (def. 1)	1.97 \pm 1.22 (1.39-3.02)	2.02 \pm 1.25 (1.37-3.05)	1.90 \pm 1.22 (1.34-2.80)

- Treatment of Bleeding Episodes

A total of 857 bleeding episodes were recorded during the study period for the 35 patients enrolled, requiring a total of 1,071 treatment days and the administration of 1,436,000 IU wilate[®]. These totals do not include the surgical procedures performed during the study period.

Table 15: Study TMAE-110 (n=35 Patients): Treatment of Bleeding Episodes (n=857)

	Mean \pm SD	Minimum	Maximum
No. of bleeding episodes / patient	24.5 \pm 8.9	1.0	39.0
No. of days of treatment / patient	30.6 \pm 10.0	3.0	51.0
No. of treatment days / bleeding episode / patient	1.3 \pm 0.4	0.9	3.0
Consumption of FVIII (IU) / patient	41,029 \pm 20,073	3,000	96,500
Dose / exposure day (IU)	1,308 \pm 409	769	2,838
Dose / exposure day per kg BW (IU)	19.1 \pm 4.4	9.7	29.4

On average, a daily dose of 19.1 IU wilate[®]/kg BW was administered to stop the bleeding. The average duration of therapy for a bleeding episode was 1.34 days.

For the 857 bleeding episodes treated, the assessment of efficacy was rated as ‘excellent’ in 52.7% of episodes, ‘good’ in 41.8% and ‘moderate’ in 5%; only 4 (0.5%) received an efficacy rating of ‘none’. The duration of each bleeding episode was \leq 2 days in more than 95 % of episodes, and \leq 4 days in 99% of all cases. Only 5 bleeding episodes needed treatment for up to 8 days. 845 of 857 bleeding episodes were resolved during the study period, 10 (1%) were assessed as ongoing and for 2 an unknown outcome was recorded.

16 patients had prophylactic treatment periods with wilate[®] with a duration of at least 4 weeks. In this subpopulation, the total number of prophylactic exposure days was 494. All patients had a baseline FVIII concentration of < 1%, i.e. were severe haemophiliacs. A total of 463 (94%) prophylactic wilate[®] doses can be regarded as successful, i.e. no haemorrhage occurred within 2 days after the administration. In 65% of cases, the administered prophylactic dose was below 20 IU/kg and may have been too low. It is worth to be mentioned that in all patients (n=8) who had a PT period of > 8 weeks in sequence, the success rate was above 90%, in 3 patients with a PT period of > 8 weeks, the success rate was 100%.

- **Treatment During Surgical Intervention**

Based on the results obtained for 3 surgeries in 2 patients, the efficacy of wilate[®] administered peri-operatively was considered to be excellent.

Overall Efficacy Conclusion for the Hemophilia A Studies

Overall the efficacy results indicated that 6 months after the initiation of treatment with wilate[®], the recovery was well within the expected range, indicating a 1.5-2.0% raise in FVIII:C plasma levels for 1 IU wilate[®]/kg BW or an absolute recovery of 60-80% after a dose of 40 IU/kg BW.

DETAILED PHARMACOLOGY

Non – clinical Pharmacological Studies

wilate[®] is a human plasma-derived blood coagulation factor concentrate (F VIII, vWF). It is indicated in the treatment and prophylaxis of bleeding in patients. The activity / potency of wilate[®] is determined and standardised in suitable in vitro tests. Animal experiments on pharmacodynamics would not add any further information.

No pharmacodynamic actions have to be expected by the trace amounts of TNBP, Triton X-100 or polysorbate 80.

Pharmacokinetics and Metabolism in Animals

No pharmacokinetic studies were performed in animals for wilate[®] itself: pharmacokinetic studies with human proteins in animals are not predictive of the situation in humans. As a foreign protein the human material is more rapidly eliminated in animals than in man.

A pharmacokinetic study was carried out by the applicant in rats, which were given 300 µg of TNBP/kg and 1,500 µg Triton X-100/kg BM i.v. The plasma half-life for TNBP was approximately 20 minutes, Triton X-100 was not detected.

According to published data [1] the plasma half-life for TNBP in rats after intravenous administration of 5 mg/kg is 1.3 hours. The main excretion route is via the urine, small amounts are excreted via faeces and the breathing air (CO₂).

There are no pharmacokinetic studies for Triton X-100 in the literature. However, the very similar nonoxynol-9 is excreted (within 7 days) via the faeces 52 – 78 %, the urine 20 – 39 % and the breathing air (CO₂) 0 – 1.2 % in rats after oral or intraperitoneal administration [2].

Recent data in the mouse have confirmed very rapid decline in polysorbate 80 levels following intravenous administration, which were reduced to less than 0.05 % after 15 minutes [3].

Human Pharmacokinetics

After injection of the concentrate, approximately two thirds to three quarters of the FVIII remain in the circulation. The level of FVIII:C should increase to 80-120% of the predicted FVIII:C.

FVIII:C decreases by a two-phase exponential decay. In the initial phase, distribution between the intravascular and other compartments (body fluids) occurs with a elimination half-life of 3 to 6 hours. In the subsequent slower phase, the half-life varies between 8 to 18 hours, with an average of 15 hours. This corresponds to the true biological half-life.

In study TMAE-101, which was conducted in previously treated hemophilia A subjects, the PK profile of wilate[®] was assessed as a surrogate marker of efficacy.

Study TMAE-101 (Hemophilia A Patients)

Study TMAE-101 was an open label, prospective study conducted in 12 previously treated patients (PTPs), aged between 18 and 56 years of age (mean age, 33 years) with severe hemophilia A (FVIII:C < 2%) who had received at least 100 past exposure days to FVIII-containing products (median previous exposure was 300 days [range, 100-900 days]).

Patients were not to receive any FVIII preparation for at least 72 hours before wilate[®] was administered at baseline or before the 6-month post-treatment PK assessment. In addition patients were not to have had an acute bleeding episode during the 72-hour washout period before the PK investigations. The dose administered was approximately 40 IU/kg BW. This was injected intravenously at a speed of 2-3 mL per minute; the total dose was to be delivered within 10 minutes.

PK parameters (AUC, C_{max}, t_{max}, t_{1/2}, MRT, Vd_{ss} and CL) were calculated from the blood samples drawn pre-dose (baseline) and then at 9 subsequent time-points up to 48 hours after treatment, at study entry and after 6 months

In vivo recovery was calculated from the peak FVIII activity measured at the start of the study and after 3 and 6 months. Baseline measurements of PK parameters are presented in the table below.

Table 16: PK of wilate[®] in Hemophilia A Patients (baseline measurements, one-stage assay)

Parameter	Mean	SD
Recovery %/IU/kg	2.04	1.15
AUC _{norm} % * h/IU/kg	37.8	10.0
Half-life (h)	14.8	3.1
MRT (h)	20.4	4.5
Clearance mL/h/kg	2.9	1.0

Key: AUC = area under the curve; MRT = mean residence time; SD = standard deviation

There were no statistically significant differences in any PK parameters with the chromogenic assay. However, AUC and CL showed the same trends as with the one-stage assays.

Human Pharmacodynamics

The FVIII/VWF complex consists of two molecules (FVIII and VWF) with different physiological functions. When infused into a hemophilia patient, FVIII binds to VWF in the patient's circulation. Activated FVIII (FVIIIa) acts as a cofactor for activated factor IX (FIXa), accelerating the conversion of factor X to activated factor X (FXa). FXa converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

Hemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of FVIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of FVIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

In addition to its role as a FVIII-protecting protein, VWF mediates platelet adhesion to sites of vascular injury and plays a role in platelet aggregation.

Immunogenicity

Immunogenicity was a safety endpoint in the 4 completed studies in previously treated hemophilia A patients. For all 4 studies, the determination of FVIII inhibitor activity (Bethesda assay) at baseline, and 3 and 6 months after initiation of treatment yielded negative (< 0.4 Bethesda Units [BU]) results for all patients on all 3 occasions.

In Study TMAE-101, there was a statistical increase of AUC between baseline and the 6-month assessment and a significant decrease of CL with the one-stage assay. All other PK parameters were not statistically significantly different over time. For the chromogenic assay, there was no difference in any parameter over time. As development of an inhibitor could lead to a reduction of AUC, this result means that there was no sign of immunogenicity of wilate[®]. The statistical test on the repeated recovery testings also revealed no statistical significance. As an inhibitor can

lead to a reduction of recovery, the interpretation here also is that there was no sign of immunogenicity.

One reason for conducting Study TMAE-108 was to establish if changes to the wilate[®] production process had affected the immunogenicity of the final product. Results from Study TMAE-108 were compared with those of Study TMAE-102, which had used batches produced before the change to the production process had been introduced. The comparison of incremental recovery (def. 1) results by both chromogenic and one-stage assays showed that higher recovery values (by approximately 15%) were observed in Study TMAE-108, indicating that there was no increased immunogenicity associated with the use of the new batches in Study TMAE-108. Likewise a comparison of the individual FVIII plasma levels indicated that the concentrations were on average 10% higher in Study TMAE-108. Although these differences were partially explained by the higher doses used in Study TMAE-108 compared with Study TMAE-102, (mean dose/kg BW/month: 190 and 163 IU, respectively), nevertheless all results strongly suggested that there was no increased immunogenicity in Study TMAE-108.

TOXICOLOGY

Administration of wilate[®] is a replacement therapy at physiological levels.

Single-dose toxicity studies in animals – the heterologous recipients – seem to be not very informative. Alterations expected are signs of volume overload (high doses), unspecific effects or sequelae of blood coagulation.

A variety of single-dose toxicity studies were performed for TNBP and Triton X-100 alone or in combination.

The lowest toxic dose of TNBP + Triton X-100 (1 + 5) was 10,000 µg/kg in rats after intravenous administration.

The human “therapeutic” dose (with 50 IU factor VIII/kg) is $\leq 2.8 \mu\text{g/kg TNBP} + \leq 5.6 \mu\text{g/kg Triton X-100}$ (sum dose $\leq 8.4 \mu\text{g/kg BM}$). These figures result in a therapeutic window / safety margin of $\frac{10,000}{\leq 8.4} = \geq 1,190$.

The polysorbate 80 content of 50 IU factor VIII/kg is negligible (0.56 mg/kg). Human volunteers tolerated 20 mg/kg i.v. without signs of toxicity [4].

Antibody formation and consequently occurrence of anaphylactic reactions are strong arguments against repeat dose toxicity studies for wilate[®] in animals.

13 weeks toxicity studies were performed by the applicant for combinations of TNBP + Triton X-100 in a broad dose range intravenously in dogs and rats. Although this was far beyond any therapeutic or prophylactic regime in patients, there were virtually no noteworthy findings.

Polysorbate 80 was used in the past (from approximately 1948 to 1979) in high doses orally in humans with lipid malabsorption and other diseases for therapeutic reasons [5].

Mutagenic Potential / Genotoxicity

According to a Note for Guidance on Preclinical Safety Evaluation of Biotechnology – Derived Pharmaceuticals [6], which also covers plasma-derived products, genotoxicity studies “are not needed”.

A great variety of genotoxicity studies – in vitro and in vivo – were run by the applicant for TNBP plus Triton X-100 or for TNBP alone. Results were always negative and this is in accordance with existing literature data.

No genotoxic effects are known regarding polysorbate 80, neither in vitro [7] nor in vivo [8].

Reproductive Toxicity

No studies were performed for wilate[®] itself. Hemophilia A patients are mainly male whereas von Willebrand disease affects both males and females. Coagulation factors, however, do not cross the placental barrier [9].

Studies on the embryotoxic and teratogenic properties of TNBP and Triton X-100 were carried out by the applicant in rats and rabbits at a wide range of i.v.-doses. The negative results are in good agreement with existing literature data.

Polysorbate 80 has also no negative effects on embryonic/fetal development in animals [10, 11].

Carcinogenicity

According to the Note for Guidance [6] mentioned above carcinogenicity studies are “generally in-appropriate”.

The repeated-dose toxicity studies and the genotoxic studies conducted by the applicant (see above) gave no evidence of carcinogenic properties of TNBP and Triton X-100. This is generally in accordance with the existing literature for TNBP. No animal studies, however, exist for Triton X-100.

Polysorbate 80 was tested in a 2-year feeding study in rats and mice at 25,000 and 50,000 ppm (corresponding to 727 – 2,535 and 1,596 – 5,098 mg/kg / day in rats and to 2,527 – 11,624 and 5,364 – 24,050 mg/kg / day in mice). There was no evidence of carcinogenicity except in male rats which showed an equivocal increase of pheochromocytomas of the adrenal medulla (control: 21 / 50; 25,00 ppm: 19/50; 50,000 ppm : 29/50) [7].

Local Tolerance

wilate[®] is well tolerated in humans, further animal experiments, therefore, are not justified.

Information on local tolerance of TNBP and Triton X-100 might be deduced from the experiments on repeat-dose toxicity (rats, dogs) and on developmental toxicity (rats, rabbits). In these animal studies the lowest dose exerting local adverse reactions was 50 + 250 µg/kg (TNBP + Triton X-100; daily injections) in dogs. At this dose 4 out of 6 dogs were affected starting in week 7 of treatment. This is far beyond any therapeutic or prophylactic regime in patients.

Polysorbate 80 is well tolerated [5].

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PART III: CONSUMER INFORMATION

wilate[®]

Human Coagulation Factor VIII (FVIII) and human von Willebrand factor (VWF)

This leaflet is part III of a three-part “Product Monograph” published when wilate[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about wilate[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Hemophilia A

Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital or acquired FVIII deficiency) and for the prevention and treatment of bleeding in minor surgical procedures.

Controlled clinical trials to evaluate the safety and efficacy of wilate[®] in major surgeries are ongoing in hemophilia A patients. Therefore, limited data are presently available on which to evaluate or to base dosing recommendations. Thus, in the case of major surgical interventions, a precise monitoring of the substitution therapy by means of coagulation analysis (FVIII:C) is indispensable.

What it does:

wilate[®] is indicated for the prevention or treatment of bleeding episodes in patients with congenital and acquired deficiency of Factor VIII (hemophilia A).

When it should not be used:

There are insufficient data to recommend the use of wilate[®] in children less than 12 years of age. There is no information on the use of wilate[®] in patients >65 years old.

What the medicinal ingredient is:

Human Coagulation Factor VIII (FVIII) and human von Willebrand Factor (VWF)

What the important nonmedicinal ingredients are:

Calcium chloride, glycine, sodium chloride, sodium citrate and, sucrose. The solvent contains Water for Injection with 0.1% Polysorbate 80

For a full listing of nonmedicinal ingredients see Part I of the product monograph.

What dosage forms it comes in:

Powder and solvent for solution for injection. One package of wilate[®] contains:

One powder vial (450 IU FVIII / 400 IU VWF or 900 IU FVIII / 800 IU VWF), a second vial containing the diluent (5 mL or 10 mL) and a Mix2Vial™ transfer set with integrated filter.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

A general risk of all blood products, from whole blood to purified coagulation factors, is the risk of transmission of viruses from the blood of the donors to the final recipients of the blood or its products. Viral safety has been a worldwide challenge during the past decade and major progress has been achieved in this area. In the particular case of wilate[®], viral safety has been increased by having included two steps of viral inactivation/removal. wilate[®] complies with the most rigid norms of viral safety in the European Union. Like other plasma products, wilate[®] carries the possibility for transmission of blood-borne viral agents like Parvovirus B19, and theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent.

BEFORE you use wilate[®] talk to your doctor or pharmacist:

- Drugs made from human blood plasma, such as wilate[®] may transmit infections, including hepatitis. Before starting treatment with wilate[®], if you have not been vaccinated against hepatitis A and B, discuss getting vaccinated with your doctor or pharmacist.
- If you are pregnant or nursing. There is no information on wilate[®] administered to nursing or pregnant women. A pregnancy test is recommended before receiving wilate[®].
- If you will be undergoing any scheduled surgical procedures.
- If you are allergic to the active substance or to any of the nonmedicinal ingredients.

INTERACTIONS WITH THIS MEDICATION

There is no known drug interaction to wilate[®].

PROPER USE OF THIS MEDICATION

Usual dose:

As dosage and treatment duration depend on your clinical situation, the type and severity of your bleeding, and your FVIII:C levels, your physician will decide on your treatment on an individual basis.

Overdose:

No symptoms of overdose with human FVIII or VWF have been reported.

Missed Dose:

It is important to take the total daily dose prescribed to ensure you get maximum benefit. If you miss a dose, take the missed dose as soon as possible, and then continue as before. However, if a dose is skipped, do not double the next dose. Continue on with your normal dose on the regular schedule as prescribed by your doctor.

Administration

wilate[®] is administered via intravenous infusion.

Instructions for Reconstitution:



Fig. 1



Fig. 2



Fig. 3



Fig. 4

1. Warm the wilate[®] powder and solvent in the closed vials up to room temperature (maximum 37°C). This temperature should be maintained during reconstitution.
2. Remove the flip caps from the wilate[®] vial and the solvent vial and clean the rubber stoppers with an alcohol swab.
3. Peel away the lid of the outer package of the Mix2Vial[™] transfer set. Place the solvent vial on an even surface and hold the vial firmly. Take the Mix2Vial[™] together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial[™] firmly through the rubber stopper of the solvent vial (Fig. 1). While holding onto the solvent vial, carefully remove the outer package from the Mix2Vial[™], being careful to leave the Mix2Vial[™] attached firmly to the solvent vial (Fig. 2).
4. With the wilate[®] vial held firmly on an even surface, quickly invert the solvent vial (with the Mix2Vial[™] attached) and push the transparent plastic cannula end of the Mix2Vial[™] firmly through the stopper of the wilate[®] vial (Fig. 3). The solvent will be drawn into the wilate[®] vial by vacuum.
5. With both vials still attached, slowly rotate the wilate[®] vial to ensure the product is fully dissolved, giving a clear or slightly opalescent, colourless or slightly yellow solution. Once the contents of the wilate[®] vial are dissolved, firmly hold both the transparent and blue parts of the Mix2Vial[™]. Unscrew the Mix2Vial[™] into two separate pieces with the vials still attached (Fig. 4) and discard the empty solvent vial and the blue part of the Mix2Vial[™].

1. Attach a plastic sterile disposable syringe to the transparent part of Mix2Vial[™]. Invert the system and draw the reconstituted wilate[®] into the syringe.
2. Once the wilate[®] solution has been transferred into the syringe, firmly hold the barrel of the syringe (keeping it facing down) and detach the Mix2Vial[™] from the syringe. Discard the Mix2Vial[™] (transparent plastic part) and the empty wilate[®] vial.
3. Clean the intended injection site with an alcohol swab.
4. Attach a suitable infusion needle to the syringe.
5. Inject the solution intravenously at a slow speed of 2-3 mL/minute.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Allergic reactions such as hives, itching, tightness of the chest, wheezing, chills, flushing, headache, feeling unusually tired, drowsy or restless, feeling sick or vomiting, and tingling of the skin, can occur with wilate[®]. If these symptoms occur contact your doctor or pharmacist for advice before continuing treatment. In rare cases, the allergic reactions are severe, known as shock or anaphylactic shock. This may include extreme difficulty breathing, or loss of consciousness. Urgent treatment is required and the emergency services should be called, for example 911.

Patients with hemophilia A may develop neutralizing antibodies (inhibitors) to FVIII. If the expected FVIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if FVIII inhibitors are present. Sometimes treatment with wilate[®] stops working due to the development of inhibitors. If you find that your usual treatment for bleeding is not working, you should contact your doctor as soon as possible. In some cases higher doses of wilate[®] or another factor VIII product are required, in other cases, alternative treatments may be prescribed by a doctor specializing in the treatment of Hemophilia.

This is not a complete list of side effects. For any unexpected effects while taking wilate[®], contact your doctor or pharmacist.

HOW TO STORE IT

wilate[®] and solvent can be stored at between +2°C and +8°C until the indicated expiry date. Within this period wilate[®] and solvent may be stored for a single block of up to 6 months at room temperature (max. +25°C). If stored at room temperature (max. +25°C) wilate[®] must either be used within 6 months or discarded. Protect from light. Do not freeze. The reconstituted solution should be used on one occasion only. Any solution remaining should be discarded.

Instructions for Injection:

As a precautionary measure, the patients pulse rate should be measured before and during the injection. If a marked increase in the pulse rate occurs the injection speed must be reduced or the administration must be interrupted.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345

Toll-free fax: 866-678-6789

By email: cadmp@hc-sc.gc.ca

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness

Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa, ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.octapharma.com>

or by contacting Octapharma Canada Inc.,

at: 1-888-438-0488

This leaflet was prepared by Octapharma Pharmazeutika Produktionsges.m.b.H

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PARTIE III : RENSEIGNEMENTS POUR LE CONSOMMATEUR

wilate[®]

Facteur de coagulation humain VIII (FVIII) et facteur von Willebrand humain (FvW)

Le présent dépliant constitue la troisième et dernière partie de la monographie de produit publiée à la suite de l'approbation de la vente au Canada de wilate[®] et est destiné aux consommateurs. Comme ce dépliant est un résumé, il ne contient pas tous les renseignements sur wilate[®]. Pour toute question au sujet de ce médicament, communiquez avec votre médecin ou un pharmacien.

AU SUJET DE CE MÉDICAMENT

Emploi du médicament :

Hémophilie A

Traitement et prophylaxie des hémorragies chez les patients atteints d'hémophilie A (déficit congénital ou acquis en FVIII) et prévention et traitement des hémorragies lors de procédures chirurgicales mineures.

Des essais cliniques contrôlés évaluant l'innocuité et l'efficacité de wilate[®] lors d'interventions chirurgicales majeures sont menés actuellement sur des patients atteints d'hémophilie A. Par conséquent, les données actuelles sont limitées pour ce qui est d'évaluer et d'établir les recommandations sur la posologie. C'est pourquoi, dans les cas d'interventions chirurgicales majeures, il est indispensable de surveiller de façon précise le traitement de substitution au moyen de l'analyse de la coagulation (FVIII:C).

Effet du médicament :

wilate[®] est indiqué dans la prévention ou le traitement des épisodes d'hémorragie chez les patients atteints d'un déficit congénital ou acquis en facteur VIII (hémophilie A).

Situations dans lesquelles il ne faut pas l'utiliser :

Les données sont insuffisantes pour recommander l'utilisation de wilate[®] chez les enfants de moins de 12 ans. Aucune information n'existe sur l'utilisation de wilate[®] chez les patients > 65 ans.

Ingrédients médicinaux :

Facteur de coagulation humain VIII (FVIII) et facteur von Willebrand humain (FvW)

Ingrédients non médicinaux importants :

Chlorure de calcium, glycine, chlorure de sodium, citrate de sodium et sucrose. Le diluant contient de l'eau pour injection avec 0,1 % de polysorbate 80

Pour la liste complète des ingrédients non médicinaux, consultez la partie 1 de la monographie de produit.

Forme posologique :

Poudre et diluant pour la solution d'injection. Un emballage de wilate[®] contient:

Un flacon de poudre (450 UI de FVIII / 400 UI de FvW ou 900 UI de FVIII / 800 UI de FvW), un second flacon contenant le diluant (5 mL ou 10 mL) et un ensemble de transfert Mix2Vial[™] avec filtre intégré.

MISES EN GARDE ET PRÉCAUTIONS

Sérieuses mises en garde et précautions

Comme avec tous les produits sanguins, du sang entier aux facteurs de coagulation purifiés, il existe un risque de transmission de virus du sang du donneur aux receveurs finaux acceptant le sang ou les produits sanguins. L'innocuité virale représente un défi à l'échelle mondiale, et ce, depuis une décennie. Des progrès importants ont été réalisés à ce chapitre. Dans le cas particulier de wilate[®], l'innocuité virale a été améliorée en intégrant deux étapes d'inactivation/de retrait des virus. L'utilisation de wilate[®] respecte les normes les plus rigides en matière d'innocuité virale dans l'Union Européenne. Comme avec les autres produits sanguins, wilate[®] est associé à la possibilité de transmission d'agents viraux transmis par le sang, comme le parvovirus B19, et en théorie, la variante de la maladie de Creutzfeldt-Jakob (vMCJ).

AVANT d'utiliser wilate[®], adressez-vous à votre médecin ou à un pharmacien :

- Les médicaments provenant du plasma sanguin humain, comme wilate[®], peuvent permettre la transmission d'infections, notamment l'hépatite. Avant de commencer le traitement par wilate[®], discutez avec votre médecin ou un pharmacien si vous n'avez pas été vacciné contre l'hépatite A ou l'hépatite B.
- Vous êtes enceinte ou allaitez. L'administration de wilate[®] aux femmes enceintes ou allaitant n'est pas documentée. Il est recommandé d'effectuer un test de grossesse avant de recevoir wilate[®].
- Vous devez subir des procédures chirurgicales.
- Vous êtes allergique à la substance active ou à l'un des ingrédients non médicinaux.

INTERACTIONS AVEC CE MÉDICAMENT

Il n'existe pas d'interaction médicamenteuse connue avec wilate[®].

UTILISATION CONVENABLE DU MÉDICAMENT

Dose habituelle :

Comme la posologie et la durée du traitement dépendent de votre tableau clinique, du type et de la gravité de vos hémorragies et de vos concentrations de FVIII:C, votre médecin décidera individuellement avec vous de votre traitement.

Surdosage :

Aucun symptôme de surdosage avec les FVIII et FvW humains

n'a été signalé.

Dose oubliée :

Il est important de prendre la dose quotidienne totale prescrite afin de s'assurer de tirer profit au maximum du médicament. Si vous oubliez une dose, prenez la dose oubliée dès que possible, et poursuivez ensuite la posologie habituelle. Cependant, si vous oubliez une dose, ne doublez pas la dose suivante. Continuez avec votre dose normale selon l'horaire régulier, tel qu'il a été prescrit par votre médecin.

Administration :

wilate[®] est administré par perfusion intraveineuse.

Instructions pour la reconstitution :

1. Réchauffer la poudre et le diluant wilate[®] dans les flacons fermés à la température ambiante (maximum 37 °C). Cette température doit être maintenue lors de la reconstitution.
2. Retirer la capsule plastique des flacons wilate[®] et d'eau pour injection puis nettoyer le bouchon de caoutchouc avec un tampon imbibé d'alcool.
3. Retirer le couvercle de l'emballage externe de l'ensemble de transfert du Mix2Vial[™]. Placer le flacon de diluant sur une surface plane et le tenir fermement. Prendre le Mix2Vial[™] avec son emballage externe et le retourner. Pousser la canule de plastique bleue du Mix2Vial[™] fermement à travers le bouchon de caoutchouc du flacon de diluant (fig. 1). Tout en tenant bien le flacon de diluant, retirer avec soin l'emballage externe du Mix2Vial[™] en faisant bien attention de laisser le Mix2Vial[™] attaché fermement au flacon d'eau pour injection (fig. 2).



Fig. 1

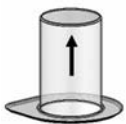


Fig. 2



Fig. 3

4. En tenant fermement le flacon de wilate[®] sur une surface plane, retourner rapidement le flacon de diluant (qui est attaché au Mix2Vial[™]) et pousser fermement le bout de la canule de plastique transparente à travers le bouchon du flacon de wilate[®] (fig. 3). Le diluant sera aspiré dans le flacon de wilate[®] par succion.
5. Les deux flacons toujours attachés, faire tourner le flacon de wilate[®] doucement pour s'assurer que le produit est complètement dissout, ce qui donne une solution claire ou légèrement opalescente, incolore ou



Fig. 4

légèrement jaune. Une fois le contenu du flacon de wilate[®] dissout, bien tenir à la fois la partie transparente et la partie bleue du Mix2Vial[™]. Dévisser le Mix2Vial[™] en deux pièces séparées avec les flacons toujours attachés (fig. 4) et jeter le flacon de diluant vide et la partie bleue du Mix2Vial[™].

Instructions pour l'injection :

En tant que mesure préventive, le rythme cardiaque des patients devrait être mesuré avant et pendant l'injection. Si une hausse marquée du pouls survient, la vitesse d'injection doit être réduite ou l'administration doit être interrompue.

1. Attacher une seringue en plastique jetable stérile à la partie transparente du Mix2Vial[™]. Retourner l'installation et aspirer le wilate[®] reconstitué dans la seringue.
2. Une fois la solution de wilate[®] transférée dans la seringue, tenir fermement le cylindre de la seringue (en la maintenant face vers le bas) et détacher le Mix2Vial[™] de la seringue. Jeter le Mix2Vial[™] (la partie de plastique transparente) et le flacon vide de wilate[®].
3. Nettoyer le site d'injection prévu à l'aide d'un tampon imbibé d'alcool.
4. Attacher une aiguille de perfusion adaptée à la seringue.
5. Injecter la solution par voie intraveineuse à une vitesse lente de 2 à 3 mL/minute.

EFFETS SECONDAIRES ET MESURES À PRENDRE

Les réactions allergiques telles que l'urticaire, les démangeaisons, l'oppression thoracique, la respiration sifflante, les frissons, les bouffées vasomotrices, les céphalées, les sensations inhabituelles de fatigue, la somnolence ou l'agitation, les malaises ou les vomissements et les picotements sur la peau, peuvent survenir avec l'utilisation de wilate[®]. Si ces symptômes surviennent, communiquez avec votre médecin ou un pharmacien afin de recevoir des conseils avant de continuer le traitement.

Dans de très rares cas, de graves réactions allergiques peuvent survenir. Il peut s'agir d'un choc ou d'un choc anaphylactique. Elles peuvent être accompagnées de difficultés extrêmes à respirer ou d'une perte de conscience. Un traitement d'urgence est requis; il faut communiquer avec les services d'urgence, le 911 par exemple.

Les patients atteints d'hémophilie A peuvent développer des anticorps neutralisants (inhibiteurs) au FVIII. Si les taux plasmatiques d'activité du FVIII ne sont pas atteints, ou si les hémorragies ne sont pas contrôlées avec une dose appropriée, un essai doit être effectué pour déterminer si les inhibiteurs du FVIII sont présents. Parfois, le traitement par wilate[®] cesse de fonctionner en raison de la présence d'inhibiteurs. Si vous vous rendez compte que votre traitement habituel pour les hémorragies ne fonctionne pas, vous devez communiquer avec votre médecin dès que possible. Dans certains cas, des doses plus élevées de wilate[®] ou d'un autre produit contenant le facteur VIII, sont requises. Autrement, différentes options thérapeutiques peuvent

être prescrites par le médecin spécialiste dans le traitement de l'hémophile.

Cette liste des effets secondaires n'est pas exhaustive. Si des effets inattendus surviennent pendant le traitement par wilate[®], communiquez avec votre médecin ou un pharmacien.

CONSERVATION DU MÉDICAMENT

Conserver wilate[®] et le solvant à une température comprise entre +2°C et +8°C jusqu'à la date d'expiration indiquée. Pendant cette période, wilate[®] et le solvant peuvent être conservés à température ambiante pour une période ininterrompue de 6 mois (max. +25°C). Si wilate[®] est stocké à température ambiante (max. +25°C), il doit être utilisé dans les 6 mois ou détruit à l'issue de cette période.

N'exposez pas le médicament à la lumière. Ne congelez pas le médicament. La solution de reconstitution doit être utilisée en une seule occasion. Toute solution restante doit être jetée.

DÉCLARATION DES EFFETS SECONDAIRES PRÉSUMÉS

Pour surveiller l'innocuité des médicaments, Santé Canada recueille des renseignements sur les effets secondaires graves et inattendus des médicaments. Si vous croyez que vous avez une réaction grave ou inattendue au médicament, vous pouvez en informer Santé Canada.

Téléphone sans frais : 866-234-2345
Télécopieur sans frais : 866-678-6789
Courriel : cadrmpp@hc-sc.gc.ca

Courrier :
Centre national des EI
Division de l'information sur l'innocuité et l'efficacité des produits de santé commercialisés
Division de l'information
Direction des produits de santé commercialisés
Pré Tunney, IA : 0701C
Ottawa, ON K1A 0K9

REMARQUE : Avant de communiquer avec Santé Canada, vous devez communiquer avec votre médecin ou un pharmacien.

POUR DE PLUS AMPLES RENSEIGNEMENTS

Le présent feuillet ainsi que la monographie de produit intégrale préparée pour les professionnels de la santé peuvent être obtenus à l'adresse suivante

<http://www.octapharma.com>
ou en communiquant avec Octapharma Canada Inc.,
au 1-888-438-0488.

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