HUMATE-P (ANTIHEMOPHILIC FACTOR/ VON WILLEBRAND FACTOR COMPLEX [HUMAN]) DOSING GUIDANCE

CSL Behring
Medical Affairs

CHOOSING AN ASSAY[1,2]

VWF:RCo measured by platelet aggregation or agglutination is considered the standard activity assay by which the international reference standard values and VWF concentrate potencies are assigned.[1]

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis of VWD[2]

RECOMMENDATION

The panel suggests newer assays that measure the platelet-binding activity of VWF (eg, VWF:GPIbM, VWF:GPIbR) over the VWF ristocetin cofactor assay (VWF:RCo) (automated or nonautomated assay) for the diagnosis of VWD (conditional recommendation based on low certainty in the evidence from diagnostic accuracy studies.)

ON-DEMAND

DOSING GUIDANCE FOR ADULT/PEDIATRIC PATIENTS WITH VWD EXPERIENCING A BLEED (SPONTANEOUS OR TRAUMATIC)

VWF

DETERMINE TYPE OF DISEASE (TYPE 1, 2, OR 3)	AFTER DETERMINING VWD TYPE, DETERMINE SEVERITY OF HEMORRHAGE (MINOR OR MAJOR)	ONCE SEVERITY OF HEMORRHAGE HAS BEEN DETERMINED, BEGIN DOSING REGIMEN (IU* VWF:RCo/KG BODYWEIGHT)	ADJUST DOSES AS NEEDED BASED ON CLINICAL JUDGMENT AND ON FREQUENT MONITORING OF THE PATIENT'S VWF AND FVIII LEVEL

VWD Type	Severity of Hemorrhage	Dosage (IU* VWF:RCo/kg Body Weight)
Type 1 VWD – Mild (baseline VWF:RCo activity typically >30%)	**MINOR** (e.g., epistaxis, oral bleeding, menorrhagia)	Typically treatable with desmopressin.
	MINOR (when desmopressin is known or suspected to be inadequate) **MAJOR†** (e.g., severe or refractory epistaxis, GI bleeding, CNS trauma, traumatic hemorrhage)	Loading dose 40-60 IU/kg. Then 40-50 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-50 IU/kg daily for up to 7 days.
Type 1 VWD – Moderate or severe (baseline VWF:RCo typically <30%)	**MINOR** (e.g., epistaxis, oral bleeding, menorrhagia)	40-50 IU/kg (1 or 2 doses).
	MAJOR (e.g., severe or refractory epistaxis, GI bleeding, CNS trauma, hemarthrosis, traumatic hemorrhage)	Loading dose 50-75 IU/kg. Then 40-60 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-60 IU/kg daily for up to 7 days.
Type 2 VWD (all variants) and **Type 3 VWD**	**MINOR** (clinical indications above)	40-50 IU/kg (1 or 2 doses).
	MAJOR (clinical indications above)	Loading dose 60-80 IU/kg. Then 40-60 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-60 IU/kg daily for up to 7 days.

* IU = International Units.

† For major bleeds in all types of VWD where repeated dosing is required, monitor and maintain the patient's FVIII level according to the guidelines for hemophilia A therapy.

SURGERY

DOSING GUIDANCE FOR PREVENTION OF EXCESSIVE BLEEDING DURING AND AFTER SURGERY IN VWD

Measure incremental *in vivo* recovery (IVR) and assess plasma VWF:RCo and FVIII:C levels in all patients prior to surgery when possible.

To determine IVR:
1. Measure the baseline plasma VWF:RCo level.
2. Infuse a calculated dose (IU/kg) of VWF:RCo product intravenously at "time 0."
3. At "time+30 minutes," measure the plasma VWF:RCo level.

Use the following formula to calculate IVR:

$$\text{IVR} = \frac{\text{(Plasma VWF:RCo}^{\text{time+30 min}} - \text{Plasma VWF:RCo}_{\text{baseline}}\text{ (IU/dL)}}{\text{Calculated dose (IU/kg)}}$$

When individual recovery values are not available, a standardized loading dose can be used based on an assumed VWF:RCo IVR of 2.0 IL/dL per IU/kg of VWF:RCo administered.

VWF:RCo AND FVIII:C LOADING DOSE CALCULATIONS FOR THE PREVENTION OF EXCESSIVE BLEEDING DURING AND AFTER SURGERY IN ALL TYPES OF VWD

Type of Surgery	VWF:RCo Target Peak Plasma Level	FVIII:C Target Peak Plasma Level	Calculation of Loading Dose (to be administered 1 to 2 hours before surgery)
Major	100 IU/dL	80-100 IU/dL	$\frac{\Delta^* \text{ VWF:RCo} \times \text{BW (kg)}}{\text{IVR}^\dagger}$ = IU of VWF:RCo required
Minor/Oral‡	50-60 IU/dL	40-50 IU/dL	$\frac{\Delta^* \text{ VWF:RCo} \times \text{BW (kg)}}{\text{IVR}^\dagger}$ = IU VWF:RCo required
Emergency	100 IU/dL	80-100 IU/dL	Administer a dose of 50-60 IU VWF:RCo/kg body weight.

BW = body weight; IU = international units;
IVR = in vivo recovery.
* Δ = Target peak plasma VWF:RCo level – baseline plasma VWF:RCo level.
† IVR = in vivo recovery as measured in the patient.
‡ Oral surgery is defined as extraction of fewer than three teeth, if the teeth are not molars and have no bony involvement. Extraction of more than one impacted wisdom tooth is considered major surgery because of the expected difficulty of the surgery and the expected blood loss, particularly in subjects with type 2A or type 3 VWD. Extraction of more than two teeth is considered major surgery in all patients.

VWF:RCo AND FVIII:C TARGET TROUGH PLASMA LEVELS AND MINIMUM DURATION OF TREATMENT RECOMMENDATIONS FOR SUBSEQUENT MAINTENANCE DOSES FOR THE PREVENTION OF EXCESSIVE BLEEDING DURING AND AFTER SURGERY

Type of Surgery	VWF:RCo Target Trough Plasma Level*		FVIII:C Target Trough Plasma Level*		Minimum Duration of Treatment
	Up to 3 Days Following Surgery	After Day 3	Up to 3 Days Following Surgery	After Day 3	
Major	>50 IU/dL	>30 IU/dL	>50 IU/dL	>30 IU/dL	72 hours
Minor	≥30 IU/dL	—	—	>30 IU/dL	48 hours
Oral†	≥30 IU/dL	—	—	>30 IU/dL	8-12 hours‡

IU = International Units.
* Trough levels for either coagulation factor should not exceed 100 IU/dL.
† Oral surgery is defined as extraction of fewer than three teeth, if the teeth are not molars and have no bony involvement. Extraction of more than one impacted wisdom tooth is considered major surgery because of the expected difficulty of the surgery and the expected blood loss, particularly in subjects with type 2A or type 3 VWD. Extraction of more than two teeth is considered major surgery in all patients.
‡ Administer at least one maintenance dose following oral surgery based on individual pharmacokinetic values. Subsequent therapy with an antifibrinolytic agent is usually administered until adequate healing is achieved.

The initial maintenance dose of HUMATE-P for the prevention of excessive bleeding during and after surgery should be half of the loading dose. Based on half-lives derived from the individual's pharmacokinetics, the frequency of maintenance doses is generally every 8 or 12 hours. In the absence of pharmacokinetic data, it is recommended that HUMATE-P be administered initially every 8 hours, with further adjustments determined by monitoring trough coagulation factor levels.

IN THE CASE OF EMERGENCY SURGERY, ADMINISTER A LOADING DOSE OF 50 TO 60 INTERNATIONAL UNITS (IU) VWF:RCo/KG BODY WEIGHT AND THEN CLOSELY MONITOR THE PATIENT'S TROUGH COAGULATION FACTOR LEVELS

1. Higgins RA, et al. Automated assays for von Willebrand factor activity. *Am J Hematol.* 2019 Apr;94(4):496-503. **2.** James PD, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv.* 2021 Jan 12;5(1):280-300.

Please refer to the enclosed full prescribing information.

For more information, contact CSL Behring-US Medical Information at 1-800-504-5434 or email: medinfona@cslbehring.com.

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