Summary Basis for Approval

Reference Number: sPLA 96-1099

Drug Licensed Name: Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized

Drug Trade Name: Humate-P®

Manufacturer: Centeon Pharma GmbH, Marburg, Germany

I. Indication for use

Humate-P® was approved under PLA 83-086 in the United States on May 1, 1986 for the prevention and control of hemorrhagic episodes in patients with hemophilia A. This application, sPLA 96-1099, was originally filed to request [redacted] to a more limited indication that the agency determined could be adequately supported by the submitted data:

> Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P is indicated (1) in adult patients for treatment and prevention of bleeding in hemophilia A (classical hemophilia) and (2) in adult and pediatric patients for treatment of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease and in mild and moderate von Willebrand disease where use of desmopressin is known or suspected to be inadequate.

Controlled clinical trials to evaluate the safety and efficacy of prophylactic dosing with Humate-P to prevent spontaneous bleeding and to prevent excessive bleeding related to surgery have not been evaluated in vWD patients. Adequate data are not presently available on which to evaluate or base dosing recommendations in either of these settings.

As of 1996, Humate-P® (trademark Haemate-P® outside of US) was approved for the hemophilia A indication in 30 countries. Humate-P®/Haemate-P® is currently approved in 28 countries worldwide for the treatment of vWD.

II. Dosage Form, Route of Administration and Recommended Dosage

Humate-P® is intended for intravenous administration only. It should be reconstituted with the supplied Sterile Water for Injection, USP and administered within three hours after reconstitution. Each vial of Humate-P® contains the labeled amount of von Willebrand factor:Ristocetin Cofactor (vWF:RCof) along with the indicated amount of antihemophilic activity (Factor VIII:C); both activities are expressed in international units. As a general rule, administration of 1 IU of FVIII activity per kg body weight will increase the circulating FVIII:C level by 2 IU/dL while 1 IU of von Willebrand Factor activity per kg body weight can be expected to lead to a rise in circulating vWF:RCof of approximately 1.5 IU/dL. Although dosage must be individualized to the needs of the patient (weight, location and severity of hemorrhage, presence of inhibitors), a general dosing regimen is recommended.

In the literature, different dosing regimens are recommended for hemophilia A and von Willebrand disease patients. The regimen for hemophilia A reflected in the revised package insert, updates the previous dosing information in order to conform to current general medical practice. The revised dosing is based on target plasma FVIII:C activity levels recommended for therapeutic replacement of Factor VIII activity for various mild to severe hemorrhagic events.

The dosing regimen recommendations for von Willebrand disease involve therapeutic replacement of von Willebrand factor for a major hemorrhagic event for mild type 1 vWD patients in situations in which desmopressin is known or suspected to be inadequate, and for minor and major hemorrhages for moderate and severe type 1 vWD patients. (Note that desmopressin can be considered to be the treatment of first choice for mild bleeding episodes *in both mild and moderate* vWF patients whose plasma Factor VIII:C activity exceeds 5%. The desmopressin acetate injection package insert states that [in such patients] "DDAVP will usually stop bleeding in mild to moderate von Willebrand's patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.") Recommendations for treatment with Humate-P for minor and major hemorrhagic events for types 2 (all variants) and 3 vWD patients are also provided in the Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized package insert. The dosing is based on IU vWF:RCof/kg body weight and recommended target plasma therapeutic levels of vWF:RCof activity.

Dosing information is provided for both adult and pediatric patients as they apply to the two different indications, vWD and Hemophilia A. Humate-P® is indicated in adults with Hemophilia A and in infants, children, adolescents and adults with vWD.

III. Manufacturing and controls

A. Manufacturing and controls:

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried Pasteurized, Humate-P® is a stable, purified, sterile, lyophilized concentrate of Antihemophilic Factor (Human) (Factor VIII). It also contains most of the spectrum of vWF multimers, including high molecular weight multimers, which are considered to be important for correcting the coagulation defect in patients with vWD.

Humate-P® is manufactured according to information contained in PLA 89-0081 approved November 20, 1996.

An update of all current release specifications and test methods for Humate-P® was provided in a supplement to PLA 83-086 on July 30, 1996 (Ref. No. 96-0972). Changes to the specifications and tests included a tightening of limits for Factor VIII:C content and pH tests as required by the European Pharmacopoeia, and tests for aluminum, albumin, vWF:RCof activity, and vWF-Antigen. These changes were approved February 5, 1997. Revisions to methods for the determination of HBsAg and residual moisture were submitted with sPLA 97-1049, filed December 2, 1997, approved September 24, 1998.

PLA 96-1099 provided support for the use of Humate-P® for the additional indication of the treatment of vWD. Additional tests to quantitate and characterize the integrity of vWF in Humate-P® have been added as specifications or lot consistency tests.

The content of vWF in Humate-P® is determined by vWF:RCof activity and vWF-Antigen (vWF:Ag) tests. The assay of vWF:RCof activity is based on the ability of vWF to aggregate platelets in the presence of the antibiotic Ristocetin A. This activity measurement reflects a physiological function of vWF and is commonly accepted as a means to quantitate the vWF potency of factor VIII/vWF preparations. The test measuring vWF:Ag employs the ——— electrophoresis method to detect vWF antigen via formation of antigen-antibody complexes. These analytical tests for vWF:RCof and vWF:Ag have been added as lot release tests. Specifications for vWF:RCof and vWF:Ag were determined from a retrospective analysis of over 50 lots of Humate-P® or Haemate-P® (see "Specifications for vWF:RCof Activity and vWF:Ag Content").

Humate-P® is a virally inactivated factor VIII concentrate that contains high-molecular-weight multimers of vWF. Considerable clinical and laboratory evidence in the literature indicates that the hemostatic effect of vWF is correlated with the content of high molecular weight (HMW) vWF multimers present in Factor VIII preparations.

Assays of the drug substance and the final container material have been validated for accuracy, precision and reproducibility. All final container lots have been shown to conform to requirements for identity, purity, potency and sterility according to 21 CFR Part 610. Three conformance lots have been submitted to CBER for testing and have been shown to meet the requirement for potency (FVIII:C and vWF:RCof), residual moisture, and sterility.

B. Viral Validation

Viral validation data for Humate-P® was submitted and subsequently approved on November 20, 1996. These data demonstrate the virucidal efficiency of the pasteurization process (10 hours at 60° C in aqueous solution) which is used in the manufacture of this concentrate. This process inactivates *in vitro* HIV and several model viruses. In each experiment, inactivation to undetectable levels of the tested virus was achieved in considerably less than 10 hours. In replicate studies, HIV was reduced by ≥5.6, ≥6.3 and ≥6.8 $\log_{10}$, respectively, to undetectable levels. In addition to HIV, studies were also performed using three lipid enveloped model viruses (HSV-1, BVDV and CMV), and one non-enveloped virus (Poliovirus). HSV-1 was reduced by ≥5.8, ≥7.2 and ≥7.3 $\log_{10}$, respectively, to undetectable levels in three replicate experiments; BVDV was reduced by ≥4.8 and ≥5.4 $\log_{10}$ to undetectable levels in two replicate experiments; and CMV was reduced by ≥6.0 $\log_{10}$ to an undetectable level in one experiment. In the case of Poliovirus, a non-enveloped virus, reduction by ≥7.1 and ≥7.3 $\log_{10}$ to undetectable levels in two replicate experiments was observed.

The viral reduction capacity of the purification and preparative steps employed in the production of Humate-P®, exclusive of the pasteurization protocol, has also been evaluated in *in vitro* experiments using HIV, HSV-1 and Poliovirus. In duplicate experiments, the mean cumulative reduction capacity for the processing

steps evaluated was found to be the following: ≥10.8 $\log_{10}$ for HIV, ≥11.1 $\log_{10}$ for HSV-1 and ≥9.1 $\log_{10}$ for the non-enveloped virus Poliovirus.

The results of the validation studies described above suggest a mean cumulative total process viral reduction capacity of up to ≥17.0 $\log_{10}$ for HIV, ≥17.8 $\log_{10}$ for HSV-1 and up to ≥16.3 $\log_{10}$ for Poliovirus for the manufacturing steps evaluated (inclusive of pasteurization).

C. Stability Studies

The approved dating period for Humate-P® stored at 2° to 8°C (36°- 46°F) is 24 months (ref. PLA 83-086).

New stability data for Humate-P® is found in Section 22(e) of sPLA 96-1099. These data support the 24 month dating period. It also includes new 6-month stability data at room temperature not exceeding 30° C (86°F) for three lots (three dosage strengths) of Haemate-P®. These data support the current six month dating for storage at 30°C (86°F) within the 24-month dating period.

Stability data is also provided for the reconstituted product stored at 20°C to 25°C for 48 hours. No significant loss in product potency was identified over the test period. However, as a measure of precaution, the reconstituted solution stored at room temperature should be used within three (3) hours.

An ongoing stability program for Humate-P®, in accordance to ICH guidelines, includes vWF:RCof activity as a key stability-indicating parameter with time points at 0, 3, 6, 12, 18 and 24 months. The available data demonstrate that vWF:RCof activity is stable to the end of the shelf-life (ref. sPLA 98-1028).

Stability data for six months storage at room temperature not exceeding 30°C (86° F) during the 24-month dating period (ref. sPLA 96-1099) and stability data for the reconstituted product stored at 20°C to 25°C for 48 hours (ref. sPLA 96-1099), include values for vWF:RCof activity and demonstrate stability of this specification.

These data support the following storage statement that is included in the package insert:

When stored at refrigerator temperature, 2° to 8°C (36°-46°F), Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P®

is stable for the period indicated by the expiration date on its label. Within this period, Humate-P® may be stored at room temperature not to exceed 30°C (86°F), for up to 6 months. Avoid freezing, which may damage the diluent container.

D. Labeling

Labeling for Humate-P® was initially approved under Label Review No. T1091703 on October 1, 1991. Revised labeling incorporating a name change of the manufacturer and distributor to Centeon Pharma GmbH and Centeon L.L.C., respectively, on a new package design was submitted to the Agency on July 30, 1996 and was approved on June 11, 1997.

The product circular has been revised to include the additional indication for the treatment of bleeding episodes patients with von Willebrand disease which resulted in a change of the proper name from "Antihemophilic Factor (Human), Pasteurized, Humate-P®" to "Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P®" This name change also resulted in a change in the NDC numbers for each strength. Changes have also been made to each section of the package insert to include new safety and efficacy information regarding the use of Humate-P® in the treatment of vWD. The sections of the package insert affected include Description, Clinical Pharmacology, Indications and Usage, Precautions, Adverse Reactions, Dosage and Administration, How Supplied, Storage and References. In addition, the product circular has been modified to incorporate all changes submitted to PLA 89-0081 regarding viral validation which is reflected in the Description section. The package insert also was revised to replace the Caution statement with "Rx only".

Dosing information for Humate-P® has been revised to include information for both the treatment of hemophilia A and for the additional vWD indication. "Pediatric Use" subsections have been added to the Precautions and Dosage and Administration sections of the package insert.

Product packaging has been revised as follows.

- As requested by the Food and Drug Administration, a description of product components is now included on the back panel of the carton.
- The values for Factor VIII and for vWF:RCof in IU/vial will be imprinted on carton and vial labels.
- The distributor's name, Centeon L.L.C. and address, have been moved from the side panels to the back panel.
- The Caution statement has been revised to "Rx only".
- The carton design reflects the FDA-approved Centeon global design.

- The revised proper names and corresponding NDC numbers replace the names and numbers that were previously on the labels which represented only FVIII:C content.

IV. Medical

The safety and efficacy of Humate-P® in the treatment of hemophilia A is well accepted. Accepted medical practice regarding the treatment of patients with vWD includes treatment with Humate-P®. Desmopressin injection (DDAVP), whose administration results in a temporary rise in FVIII:C and vWF:RCof levels is approved for use in hemophilia A patients with plasma levels of FVIII:C at least 5% of normal. Desmopressin injection is also indicated in mild and moderate type I vWD patients whose FVIII:C levels are greater than 5% of normal for perioperative use and to treat spontaneous or trauma-induced bleeding. The package circular for DDAVP injection states that "Those von Willebrand's disease patients who are least likely to respond are those with severe homozygous von Willebrand's disease with factor VIII coagulant activity and Factor VIII von Willebrand factor antigen levels less than 1%. Other patients may respond in a variable fashion depending on the type of molecular defect they have. DDAVP is not indicated for the treatment of severe classic von Willebrand's disease (Type I) and when there is evidence of an abnormal molecular form of factor VIII antigen."

Humate-P® is used more frequently in the United States for the treatment of vWD than for the treatment of hemophilia A. Post-marketing surveillance data (Section 22 (d) 12, Volume 12, Page 001), has demonstrated that Humate-P® has a very satisfactory safety profile for both viral and non-viral adverse events in hemophilia A and vWD patients. In addition, several published studies have shown that Humate-P® corrects hemostatic defects in vWD patients without significant adverse effects.

Three clinical reports have been provided in this application that together document the safety and efficacy of Humate-P® in the treatment of bleeding episodes in patients with vWD.

1. Program 7CDN501VW: Report of the safety and efficacy of Haemate P® in Canadian vWD patients

A retrospective review contains safety and efficacy information collected for Canadian patients with vWD who received Haemate-P® (modified manufacturing process, reference PLA Supplement 89-0081) under the Emergency Drug Release Program (EDRP), a program administered by the Health Protection Branch (HPB), Canada. In this open, uncontrolled program, retrospective data collection was performed by, 1) retrieval from source data, which provided the primary patient population, and 2) retrieval by structured interview via telephone and/or

facsimile which provided the secondary patient population. Either patients were required to provide permission prior to review of their medical records for the purpose of transcribing information to case report forms (CRFs), or the local Institutional Review Board (IRB) had to give approval of data collection without informed consent. For the primary patient population, clinical safety and efficacy data were confirmed from source documents and collected retrospectively on a standardized data collection form. The data from the sponsor's retrospective data collection forms were compared for consistency to [redacted] data collection forms that were completed for a subset of patients around the time of product administration. The results from Centeon and [redacted] data were generally concordant. The sponsor did not conduct quality assurance site audits to evaluate the quality of the on-site retrospective data collection process. FDA conducted Bio-Research monitoring inspections of three primary population physician sites.

The overall response to Haemate-P® administration for each primary patient was classified by the treating physician at the time of the retrospective data collection according to definitions for each treatment type (surgery, bleeding, other uses or prophylaxis). Adverse events (regardless of the relationship to the study product) were also recorded.

The definitions of overall response to Haemate-P® administration was classified to the following scheme:

Excellent:	hemostasis achieved/cessation of bleeding
Good:	slight oozing/adequate control of bleeding; did not require additional product for unplanned treatment.
Poor:	moderate bleeding/moderate control of bleeding; required additional product for unplanned treatment.
None:	Severe uncontrolled bleeding.

Twenty-five different lot numbers of Humate-P and of Haemate-P were recorded as administered under the Canadian ERDP. In addition, six lot number of product were recorded but did not match any of the sponsor's known lot numbers. Five patients received Humate-P (manufactured by the process approved in the US under PLA 83-086) rather than Haemate-P.

Fifty-three out of 106 (50%) of physicians identified as secondary centers failed to provide any follow-up data for authorizations granted.

Seven hundred and fifty-four (754) authorizations to ship Haemate-P® for treatment of patients with vWD under EDRP, were identified and an attempt was made to follow the disposition of all authorizations granted between 22 November 1991, the start of the Canadian EDRP, and 30 April 1996, the data-collection cut-off date. There were 514 requests for product use for surgery, bleeding or prophylaxis in 97 Canadian patients for whom on-site data was obtained (verified from source documents). Of these, product was not used in 151 cases, and follow-up safety and/or efficacy information was retrospectively obtained for 303 (83%) of the remaining 363 requests. Eleven out of 23 primary centers had source data for at least one treatment authorization unavailable or unverifiable, either because of lack of treating physician cooperation in providing data, lack of informed consent, or because patient medical records were not located during Centeon's site visits. In 158 requests for which the sponsor had its own retrospectively collected data, the sponsor was also able to provide, at FDA request, the results from the [illegible] data collection sheets, an earlier data collection effort that was conducted at the time of the ERDP authorizations. Single page [illegible] Canada data collection forms were requested to be filled out by the treating physician and returned to the earlier sponsor. These [illegible] Canada data collection forms were provided to the authorizing [requesting/treating] physician at the time of the HPB authorization, and have spaces/boxes for MD overall rating of the product as "EFFECTIVE - NO, YES," and "SAFE - NO, YES," with 4 lines each under Efficacy and under ADVERSE REACTIONS (ADE) headings to record comments. Approximately one-half of these original [illegible]. Canada data collection forms were apparently returned to [illegible] and made available to the sponsor, despite return of the completed data collection forms being a requirement of distribution of the product under the ERDP.

In many cases, product from one request was used for several treatment courses in one patient. Therefore, there are more reported treatment courses than requests ("authorizations").

Because information concerning laboratory parameters, including baseline and post-infusion vWF:RCof and FVIII:C levels was scanty in the original submission, the sponsor attempted to collect additional laboratory data at FDA's request from two of the sites with the largest numbers of authorizations. These data were combined with previously-submitted laboratory data and submitted in November, 1997. Plasma vWF:RCof and FVIII:C activity levels pre- and post-infusion were available for only 22 and 20 patients, respectively. Keeping in mind that the timing of blood sampling and analysis methods were non-standardized, the observed mean *in-vivo* recovery (IRV) values obtained from this limited Canadian data set were 1.42 +/- SD 0.78 IU/dL vWF:RCof per IU/kg administered and 2.64 +/- SD 2.04 IU/dL FVIII:C per IU/kg administered. The

IVR results were similar to those seen in the interim analysis of the pharmacokinetic study being performed by Dr. Juan Chediak (see below) in the case of FVIII:C and somewhat lower than Dr. Chediak's interim results in the case of vWF:RCof.

Comparisons of data submitted by the sponsor to FDA against data in patient medical records were made for patients treated at three sites that were the subject of FDA BioResearch Monitoring inspections.

Five patients received Humate-P® (manufactured by the process approved in the US under PLA 83-086) rather than Haemate-P®.

Efficacy:

Clinical efficacy of Humate-P in the control of bleeding in patients with vWD was determined by a retrospective review of clinical safety and efficacy data obtained from 46 bleeding patients drawn from the 97 "primary population" Canadian vWD patients (54 adults and 43 pediatric patients) who were provided with product for bleeding, surgery, prophylaxis, or other use under an Emergency Drug Release Program. Dosage schedule and duration of therapy were determined by the judgment of the medical practitioner.

Humate-P® was administered to 97 patients, in 530 treatment courses: 73 for surgery, 344 for treatment of bleeding and 20 for prophylaxis of bleeding. For 93 "other" uses, the majority involved dental procedures, diagnostic procedures, prophylaxis prior to a procedure, or a test dose.

Of the 97 patients in the primary population, 58 were male and 39 were female. A breakdown by gender, age, and weight by diagnostic subtype of vWD is presented in the submission. The mean age for all patients was 28.6 years (range 0.4-81.1 years). The mean body weight for all primary population patients was 56.1 kg (11.3 - 113.6 kg). Among the 14 patients listed in the "other" diagnostic category, 9 have unknown diagnoses, 4 acquired vWD, and 1 type 1 vWD combined with severe factor IX deficiency.

A summary of the number of patients and bleeding episodes treated, by vWD type, and corresponding efficacy rating is provided in Table 1. The efficacy rating was excellent/good in 100% of bleeding episodes treated in type 1, 2A and 2B patients. In type 3 patients, 95% of the bleeding episodes were rated as excellent/good and a poor (or no) response was observed in the remaining 5% of bleeding episodes treated. Eighteen out of 21 (86%) type 3 patients were reported to have excellent/good responses and three (14 %) were reported to have at least one poor or "none" response rating.

Table 1: Summary of efficacy for bleeding episodes - all patients*

	Diagnosis							
	Type 1 vWD		Type 2A vWD		Type 2B vWD		Type 3 vWD	
NUMBER OF PATIENTS	13		2		10		21	
Excellent/good	13	100%	2	100%	10	100%	18	86%
Poor/none	-	-	-	-	-	-	3	14%
NUMBER OF EVENTS	32		17		60		208	
Excellent/good	32	100%	17	100%	60	100%	198	95%
Poor/none	-	-	-	-	-	-	10	5%

*The total number of bleeding events among Types 1, 2A, 2B, and 3 vWF patients was 317. An additional 27 bleeding events were treated among patients with unknown, acquired or "other" bleeding disorders.

For pediatric patients a summary of the number of patients and bleeding episodes treated, by vWD type, and corresponding efficacy rating is provided in Table 2. The efficacy rating was excellent/good in 100% of bleeding episodes treated in infants (types 2A, 3), children (types 1, 2A, 2B) and adolescents (types 1, 2B). In type 3 children and adolescents, 90% and 96% of the bleeding episodes were rated as excellent/good and a poor/none response was observed in the remaining 10% and 4% of the bleeding episodes, respectively. Three of nine type 3 patients had at least one treatment course response rated poor or "none."

Table 2: Summary of efficacy for bleeding episodes - pediatric patients

	Diagnosis							
	Type 1 vWD		Type 2A vWD		Type 2B vWD		Type 3 vWD	
NUMBER OF PATIENTS	4		2		5		12	
Excellent/good	4	100%	2	100%	5	100%	9	75%
Poor/none	-	-	-	-	-	-	3	25%
NUMBER OF EVENTS	8		17		22		138	
Excellent/good	8	100%	17	100%	22	100%	128	93%

Poor/none	-	-	-	-	-	-	10	7%

The dosing information (all patients) for bleeding events is summarized in Table 3.

Table 3: Summary of dosing information for bleeding events

		Type/location[1]				
		Digestiv System	Nose + Mouth + Pharynx	Integument System	Female Genita System	Musculo-skeletal
No. of Patients		14	29	11	4	22
Loading dose (IU vWF:RCof/kg)	Loading doses[2]	37	127	22	7	107
	Mean	62.1	66.9	73.4	88.5	50.2
	SD	31.1	24.3	37.7	28.3	24.9
Maintenance Dose (IU vWF:RCof/kg)	Maintenance doses[1]	250	55	4	15	121
	Mean	61.5	67.5	56.5	74.5	63.8
	SD	38.0	22.4	63.3	17.7	28.8
No. of treatment days per event	No. of Events	49	130	22	9	108
	Mean	4.6	1.4	1.1	2.8	2.0
	SD	3.6	1.2	0.4	2.9	1.9
No. of Infusions/da						
Day 1[3]	No. of Patients	14	29	11	4	22
Day 1	No. of Events	49	130	22	9	108
	Mean (# of infusion	1.2	1.1	1.0	1.0	1.0
	SD	0.4	0.2	0.2	0.0	0.1
Day 2	No. of Patients	13	9	3	1	15
Day 2	No. of Events	41	12	3	1	26
	Mean (# of infusion	1.2	1.3	1.0	1.0	1.2
	SD	0.6	0.5	0.0	-	0.5
Day 3	No. of Patients	12	6	-	2	10
Day 3	No. of Events	25	9	-	3	18
	Mean (# of infusion	1.5	1.4	-	1.0	1.2
	SD	0.8	0.7	-	0.0	0.4

[1]Several patients had bleeding in more than one site on the same or different occasions.
[2]Number of infusions where the dose per kg body weight was available.
[3]Day 1 = First treatment day

There were 58/303 authorization instances in which one day was skipped during the treatment of a particular episode/indication. It could not be determined whether skipped therapy days may be indicative of unplanned resumption of product infusions in response to undocumented re-bleeding. There did not appear to be a set pattern to when during a treatment course skipped days occurred (early, middle, or late in the course). –

A per-patient analysis of efficacy outcomes was not included in the original submission but was submitted at FDA request in August and October, 1997.

No patients/authorizations in any category for any indication were rated as "none" for the efficacy response.

The only authorizations rated "poor" among the primary population were as follows:

1/15 (6.7%) type 2B surgery authorizations

10/209 (4.8%) type 3 bleeding authorizations

The line listing table 3, appendix IV to the study report was examined and it was verified that there were 11 authorization-indications (treatment) rated "poor." The four patients contributing to "poor" efficacy outcomes for a total of 11 authorizations are described as follows:

Patient # —

This was a male type 3 vWD patient who was described as having a poor response to two infusions of product on treatment day 1 and one infusion on day 2 for treatment of epistaxis. Patient received 500 IU FVIII:C / 15.5 kg = 32.2 IU/kg of lot #015641 for each infusion. Prior and subsequent treatments for bleeding numbered 23, and were all said to result in excellent response. No adverse events (AEs) were reported.

Patient # —

This female type 2B vWD patient had one poor response to a single

infusion of product for surgery (dental extraction). Patient received 1000 units FVIII:C/43 kg = 23.2 IU/kg of an unknown lot #. All prior and subsequent treatments totaling 7 were said to result in an excellent response. No AEs were reported.

Patient # ~

This female type 3 vWD patient is described as having 3 poor responses to product administration for left elbow bleeds. The first poor response was to a single infusion of 500 IU FVIII:C/20 kg = 25 IU/kg of an unknown lot #. The 2nd poor response was to 5 consecutive days of infusion of 500 IU FVIII:C/27 kg = 18.5 IU/kg per day of lot #0756641. The 3rd poor response recorded was to 8 infusions over nine days of 500 IU FVIII:C/30 kg = 16.7 IU/kg per infusion of lot #2476641. It is recorded that all prior and subsequent treatments totaling 45 uses which included treatment of elbow, head, and nose bleeds, prophylaxis for elbow bleeds, and surgical use for port-a-cath insertion and dental extraction resulted in either good or excellent responses. This subject received a huge number of infusions. No AEs were reported.

Patient # —

This male type 3 vWD patient had 6 poor responses to treatment of bleeds (2 GI, 2 right ankle, 2 epistaxis). Poor ratings were assigned in response to a course of 5 daily infusions of 750 IU FVIII:C/33 kg = 22.7 IU/kg for GI bleeding. The patient then immediately received 1 pre- and 4 daily post-colonoscopy doses for which he received a good rating, then, starting the next day after the last post-colonoscopy dose, the patient received a further 4 days of 750 IU FVIII:C/33 kg = 22.7 IU/kg infusions/day for GI bleeding, for which the product efficacy rating was poor. The next poor rating was given for ankle bleeding for a course of 7 infusions of 750 U FVIII:C/32 kg = 23.4 IU.kg each over a 15 day period, commencing with 2 infusions on the first day, followed by a 5 day hiatus before qod-q3d infusions were resumed. A poor rating was given in response to 6 infusions (3 of 500 IU FVIII:C/32 kg = 15.6 IU/kg of lot #0756641 and lot #025641, followed by 3 of 750 IU FVIII:C/32 kg = 23.4 IU/kg of the former lot #, plus lot #055641, and #1326641) given for epistaxis over a 14 day period. A poor response was recorded for 2 consecutive daily infusions of 750 IU FVIII:C/46.5 kg = 16.1 IU/kg of lot #3056641 for epistaxis, and for 12 infusions of 750 IU FVIII:C/45.6 kg = 16.4 IU/kg each over a period of 33 days for an ankle bleed (all infusions lot #3336641, except the 6th infusion was combined from lot #3056641 and #3336641). It is recorded that all prior and subsequent treatments totaling

50 uses for prophylaxis, various bleeds, and dental extraction resulted in either good or excellent responses. This could be taken to imply that the treatments associated with poor responses were clustered, when in fact good or excellent treatment for epistaxis or right ankle bleeding episodes were sandwiched in between poor treatment responses. Reported AEs for this patient included mild chills, paresthesia, and vasodilatation.

Of the above 4 patients, only # — appears to have been under-dosed, in terms of the sponsor's draft labeling guideline ( ). Of note, of the 11 treatment courses given poor efficacy ratings, 2 were with unknown lot numbers. There did not appear to be a common pattern across different patients of lot the same numbers eliciting poor responses.

Of note, patient #283 had the only unplanned treatment infusion in the primary patient cohort. This type 1 patient received a total of 2 infusions for an elbow bleed, the 2nd being unplanned. The authorizing physician appears to have violated the retrospective data collection instructions and classified the efficacy of this treatment episode as "excellent." The protocol required no better than a "poor" efficacy evaluation when unplanned further treatment infusions needed to be administered. No AEs were reported.

Five authorization-indications out of 54 (9.2%) among 28 type 3 patients were rated "unable to assess, " as was 1 of 7 authorization-indications among the 14 patients in the "other" diagnostic category whose indication was listed as "other." Authorizations rated "not applicable" included patients receiving a test dose, presumably to determine half life and recovery prior to dosing for an elective procedure, and in the case of patient #75, a lumbar puncture. Patients whose treatments/uses of product were rated "unable to assess" are:

Patient #	**Indication**
—	bleeding, tongue
—	bleeding, GI Colonoscopy
—	bleeding, GI (following R hemicolectomy for which treatment was rated "excellent")
—	other, abdominal pain - presumably bleeding liver tumor. This subject was rated "unable to assess" for 4 separate authorization episodes for abdominal pain, two of which are captioned as above or

"presumed bleeding in liver."

other, prophylaxis (following "excellent" response under same authorization for bleeding, vaginal.

From the [redacted] data collection sheets, which reported overall safety and efficacy assessments of the treating physicians on a product request basis rather than on a treatment course basis, the product was judged effective in 319/334 cases (96%). These overall results agree closely with the results of Centeon's retrospective data collection. There is no distinction between primary and secondary patient populations in the case of the [redacted] data. The latter database included safety and efficacy results for 83 product requests for which Centeon LLC lacked data from its own data retrospective data collection efforts. In the primary population, 158 product requests had data from both manufacturers' data collection sheets, in the secondary population, 94 product authorizations had data provided from both sources. In the [redacted] database, the product was judged safe in 322/334 requests (96%). Combining data from both sources, safety and efficacy data were missing for 11% of primary database patients.

Canadian secondary population.

Data for the Canadian secondary population were collected by telephone and by facsimile transmission and were not verified by site visit. No information was provided as to whether unplanned infusions were administrated among the secondary cohort patients, which might suggest a lack of/reduced efficacy. A more limited number of data elements/fields were presented in the data listings for the secondary population compared to the primary population. For example, the only data listings for the secondary patient population appear in tables 1 and 6 of appendix VI. The only fields presented are authorization #, date of authorization, physician name, patient initials, total amount infused per authorization, type of vWD, indication for use, overall efficacy per authorization (not per treatment), AE description, AE relationship to product, and comment field.

The sponsor presents data on 96 secondary population subjects, whose vWD diagnostic subtype breakdown is as follows:

vWD Type:		I	2A	2B	3	Other
No. Pts	66	1	10	2	17	
No. Authorizations		85	1	12	3	33
No. Indications by		not provided.....				

Authorization

Overall, among the 27 authorizations for bleeding, the physicians rated the authorization use outcome excellent in 56% (15/27) of cases, good in 22% (6/27), poor in zero %, none in 11% (3/27), "unable to assess" in 11% (3/27), and "not applicable in zero %.

It should be noted that secondary population physicians did not use the requested efficacy rating system for 22 authorizations that were rated either "excellent/good" or "effective" and for 3 authorizations rated "poor/none."

Ten authorizations (8%) among 6 (6.2%) secondary cohort patients were rated poor or none for efficacy response. These were reviewed in detail. Details are as follows:

Patient —, (FDA code number; the sponsor did not assign patient numbers to the secondary population), a male patient with vWD type I, received a total of 70,000 IU FVIII:C of product for tricuspid valve replacement. The patient required cyroprecipitate and Amicar to stop bleeding; efficacy of Haemate P was rated "poor." No AEs were reported.

Patient —, a male with acquired vWD type I related to leukemia, was given 12,000 IU product for surgery. The patient required 3 additional infusions totaling 55,000 IU for recurrent GI bleeding occurring on post-op days 8, 10, and 24. Efficacy was rated as "poor/none." for each of the 3 infusions. No AEs were reported.

Patient — , a female type I patient, received 16,000 IU Haemate P for surgical and postoperative coverage. Re-bleeding occurred 4 days post-op. During the ensuing 10 days, 25,000 IU was administered. A second re-bleed occurred 15 days post-op. An additional 8,500 IU was administered. Efficacy was rated "poor" for the first and 2nd courses and excellent for the 3rd course given for the 2nd bleed. No AEs were reported.

Patient — a male with acquired vWD and a history of anti-vWF antibodies for at least 2 years prior to receipt of any therapy, received product at 4, 10, 25, and 50 U/kg (total of 20,000 IU) in preparation for retinal surgery. Activity of vWF rose only 10-12% at 25 U/kg and 25% at 50 U/kg. Efficacy was rated "poor." Subsequently, immunosuppressive therapy and IVIG were used successfully to normalize vWF activity. Upon tapering prednisone, FVIII:C and vWF activity declined as the inhibitor titer rose. Following prednisone plus cyclophosphamide, no further recurrence of the inhibitor was observed. No AEs were reported.

Patient — a female patient described as having vWD of unknown type was rated as having "poor" responses to infusions of 2,750 and 2,000 IU for

suprapubic vesicatomy, due to continued oozing and a hematoma around the suprapubic tube. An "excellent" response was recorded after 4,500 IU product received, but the bleeding resolved after the suprapubic tube was withdrawn. The haematoma was reported as an AE unrelated to product.

Patient [redacted], a male with vWD type 1, received 5,100 IU for surgery, had post-op bleeding, and the product efficacy was rated as "poor" for the authorization. No AEs were reported.

Three authorizations among 2 patients who received product for bleeding indications were rated "unable to assess." Details are as follows:

One (authorization [redacted]) male IIB vWD patient who was reportedly receiving didanosine died of hemorrhagic pancreatitis. This patient is recorded as having received 1,000 U of product during his brief hospitalization for an acute abdomen.

One male patient (authorization [redacted]) received 12,250 IU for bleeding and had multiple treatments; the sponsor gave the latter as the reason that the efficacy was recorded as "unable to assess." The same patient also received authorization [redacted] 7 under which he received 22,000 IU for bleeding and had multiple treatments; the sponsor gave the latter as the reason that the efficacy was recorded as "unable to assess." The sponsor was requested to count these authorizations as "none" for efficacy and reanalyze the secondary population results accordingly, which was accomplished.

The results of the Canadian retrospective study, taken in conjunction with the interim results of the pharmacokinetic data from the study being performed by Dr. Chediak, support the efficacy of Humate-P in the treatment of spontaneous and trauma-induced bleeding. It is recognized that the product provides replacement therapy in patients with inadequate plasma von Willebrand's factor activity. Had the product been less effective, one might have anticipated a lower number of treatment courses that were comprised of a single infusion.

The extent to which one may rely on pharmacokinetic data to support the efficacy of a product used for replacement therapy is in part contingent on being able to demonstrate replacement to levels of the clotting factor associated with normal clotting function in unaffected individuals, and on having an assay that correlates well with, and is sufficiently specific for normally-functioning clotting factor. Although it was concluded at an FDA-NIH workshop on vWF that products for use in vWD should be assayed using vWF:RCof, it is unknown whether this assay precisely quantities all of the pertinent bioactivity of Factor VIII/vWF complexes in vivo. There have been instances in which FDA has required demonstration of

clinical efficacy endpoints with products intended for replacement therapy prior to licensure (recombinant human growth hormone and human insulin serve as examples).

In the case of peri-operative use of Humate-P in the Canadian retrospective experience, the variability of the length of treatment for even the same type of surgery underscores the lack of knowledge concerning optimal peri-operative dosing in vWF. In a teleconference with the sponsor held 4 April 1997, the sponsor's representatives concurred with others' concerns regarding the likelihood that the plasma elimination half-life of vWF:Rcof may shorten in the immediate post-operative period of major surgery, due in part to accelerated consumption. The sponsor has committed to conducting a phase IV surgery which will measure plasma activities pre- and post- product administration following a test dose in the non-bleeding state and during surgery and to attempt to correlate trough levels of vWF:RCof and FVIII:C with hemostatic variables (see below).

Safety:

Allergic symptoms, including allergic reaction, urticaria, chest tightness, rash, pruritus, and edema, were reported in 6 of 97 (6%) of primary population patients in this Canadian retrospective study. Two of 97 (2%) experienced other adverse events that were considered to have a possible or probable relationship to the product. These included chills, phlebitis, vasodilatation, and paresthesia. Sixteen of 97 primary population patients reported one or more adverse experiences. Adverse events reported include injection site pain, swelling, phlebitis or rash (6 subjects), stupor, hypoxia, generalized pruritis, blurred vision, chest pain, and diarrhea. The subject with stupor and hypoxia had undergone laparoscopic cholecystectomy and was reported to have mild wheezing and gasping for breath on the day of surgery that was treated with nasal oxygen. She later was noted to be difficult to arouse and reportedly responded to naloxone. On treatment day 12, she was noted to have a mild rash on her forearm and upper chest, generalized pruritis, headache, edema, mild chest tightness, and blurred vision. Her symptoms resolved with IV antihistamine and hydrocortisone. Treatment was stopped the next day when she was noted to have a red hot edematous area on her arm and complained of recurrent pruritis. One patient died from injuries sustained in a motor vehicle accident; this patient's death was not considered to be related to the administration of product. All adverse events with the exception of the one death were mild or moderate in intensity. Among the 96 secondary patients, five (5%) experienced an adverse event. A total of seven adverse events were reported of which three were considered related to study product. These included hyponatremia in one patient and rash and fever in a second patient. Adverse experiences not considered by the treating physician to be related to administration of product included death due to hemorrhagic pancreatitis in a

subject who reportedly received concomitant didanosine, hematoma, hypotension, and rash. In both primary and secondary population analyses, adverse events were only captured if they occurred within 24 hours following product administration. In the case of post-operative patients, adverse events consisting of nausea, vomiting, fever, and operative-site pain were omitted from the sponsor's retrospective data collection activities.

Adverse events were reported for 14% of pediatric patients. AEs judged by the investigator to be product-related were reported for only two pediatric patients, were mild in intensity, and were identified as chills, phlebitis, vasodilatation, and paresthesia.

In spite of missing data, no selection bias in defining the primary patient population was evident, as reflected by the comparable safety and efficacy findings in the primary and secondary patient populations. (The primary patients population data were collected from sites having at least three product use authorizations per site.)

The full study report is found in Section 22(d) 11.A of this submission (Volume 3, Page 001). Amendments to the report were submitted August 10, 1997, October 29, 1997, and January 23, 1998.

Bioresearch Monitoring Inspections:

Inspections of three clinical investigators were performed by an inspector from CBER/FDA in support of the subject PLA. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. Copies of information for select subjects were obtained from the PLA, and were compared with source documents during the inspections. The inspections focused on subjects enrolled in Program (7CDN501 v W), Survey of the Efficacy and Safety of Humate-P® in Canadian von Willebrand disease patients, and included specific questions concerning the study. The results of bioresearch monitoring inspections of three clinical sites indicate that the deviations made by the clinical investigators are not substantive and that the submitted data can be considered reliable and accurate.

2. **Study BI 8.021-7S--501XX: Humate-P® (Haemate-P®) pharmacokinetic comparison of batches produced with the original method and with the modified manufacturing process**

Twelve Swedish patients, four with hemophilia A and eight with vWD, were evaluated in an open, controlled, retrospective study to compare the

pharmacokinetic variables of Humate-P® between the "original" and "modified" manufacturing processes. In this trial, the "original" process was that approved in the US for the manufacture of Humate-P® (PLA 83-086), which utilizes 100% US source plasma. The "modified" process is that described for Humate-P® in PLA Supplement 89-0081, but utilizes product (Haemate-P®), which is produced from 80% US and 20% non-US source plasma. As part of this trial, factor VIII:C and vWF:RCof half-life and recovery were determined in the vWD patients.

Diagnosis types for the eight vWD patients were as follows: one with type 1 (moderate), one with type 2A, and six with type 3. Patients ranged in age from three to 42 years. Of the eight patients, five initially received Humate-P® manufactured by the original method (PLA 83-086) and subsequently received Haemate-P® produced by the modified method (PLA Supplement 89-0081). Two patients received Haemate-P® (modified process) and another product (AHF-Kabi), and one received Haemate-P® (modified process) only. The mean dosages of factor VIII and vWF:RCof administered to the vWD patients were 17.6 IU/kg and 23.3 IU/kg, respectively, for Humate-P® (original process) and 13.1 IU/kg and 19.4 IU/kg, respectively, for Haemate-P® (modified process). Blood samples were collected prior to infusion and at 30 minutes and 23-24 hours post-infusion.

The therapeutic activity response in the vWD patients gave a mean vWF:RCof activity rise/IU/kg of 3.35 (range 2.62-3.97 among 5 subjects) for Humate-P® (original process) and a mean rise/IU/kg of 3.31 (range 1.87-6.29 among 8 subjects) for Haemate-P® (modified process). These rises in vWF:RCof activity are consistent with the expected rise determined from the literature. These responses were calculated using the subjects' plasma vWF:RCof activity as measured by the Swedish investigator, in conjunction with the sponsor's measurements of product vial vWF:RCof content. When the Swedish investigator's measurements of product vial vWF:RCof content were used instead, higher values for the mean vWF:RCof activity rise/IU/kg body weight of product administered were obtained. Similar results were observed for half-life. While this study did not demonstrate any difference between the results from Humate-P®/Haemate-P® produced by the two manufacturing processes, the study was judged inadequate to demonstrate the bioequivalence of the two formulations. Because only three of eight vWD subjects in this study had more than two post-baseline time point samplings of vWD:RCof activity, this study could not be used to determine the half-life of vWD:RCof activity. Because the study was performed in non-bleeding subjects, the design of the study did not address the question of whether the pharmacokinetics of the product, including the half-life, might be clinically significantly altered during major hemorrhage.

Among the 12 Swedish patients who received Humate-P® and Haemate-P® in this trial, none reported an adverse event.

The full study report is found in Section 22(d) 11.B of this submission (Volume 10, Page 002).

3. Pharmacokinetic Study of the use of Humate-P®, Antihemophilic Factor (Human), Dried, Pasteurized, in Patients with von Willebrand's Disease

Interim results from a clinical trial conducted by Dr. J. Chediak at the Illinois Masonic Medical Center, under [redacted] were submitted under this supplement on December 1, 1997. This study entitled "Pharmacokinetic Study of the Use of Humate-P®, Antihemophilic Factor (Human), Dried, Pasteurized, in Patients with von Willebrand Disease" was an open-label, single-center, single-infusion study to evaluate the safety and pharmacokinetics of Humate-P® (approved process) in patients with severe type 1, type 2A, or type 3 vWD. Laboratory assessments included Factor VIII:C levels (for determination of activity, recovery, and time course), vWF:Ag levels, bleeding time (BT), vWF:RCof activity (for determination of activity, recovery, and time course), and platelet vWF assay.

The pharmacokinetics of Humate-P® have been evaluated in 8 vWD patients [type 1, n=1; type 2, n=1; type 2A, n=4; type 3, n=2] in the non-bleeding state. The median half-life of vWF:Rcof was 10.3 hours (range: 6.4 to 13.3 hours). The median *in vivo* recovery for vWF:RCof activity was 1.89 (IU/dL)/(IU vWF:RCof /kg) [range: 1.10 to 2.74 (IU/dL)/(IU/kg)]. In all subjects, the administration of Humate-P® resulted in a transient shortening of the bleeding time. Humate-P® was effective in improving the vWF multimer pattern in vWD patients and in most cases this improvement was sustained through 22 to 26 hours postinfusion

4. Additional pharmacokinetic data

The sponsor submitted a report combining data from an open, uncontrolled prospective pharmacokinetic evaluation of the product in 23 Japanese subjects together with data from an open, uncontrolled retrospective evaluation of 5 German subjects with vWD. Because it could not be documented as to whether the Japanese study had been conducted with the informed consent of the subjects, the sponsor withdrew the Japanese study results from supporting the efficacy of the product in the application.

Clinical Trials Post-Licensure

The sponsor commits to conducting an additional clinical trial evaluation of Humate-P® (PLA 89-0081 upon approval) in patients with vWD in the United States. The study

protocol submitted December 22, 1997 with [redacted] has been revised following a July 21, 1998 meeting with the FDA.

This study will evaluate the safety and efficacy of Humate-P® when administered to patients with mild, moderate, or severe vWD undergoing an elective surgery. [redacted]

Additional Safety Data

As part of the safety evaluation of Humate-P®, the sponsor has provided an analysis of reports obtained through postmarketing surveillance of spontaneous adverse reactions. Fifty-four individual case reports were received between February 1, 1990 and April 25, 1996. The distribution of individual reports by disease state was as follows: 33 hemophilia A, 19 vWD, and two not identified. Of the 19 reports associated with use for vWD, 10 (53%) were related to suspected viral transmissions and 9 (47%) were related to nonviral transmission symptom classes.

The types and frequency of reported adverse experiences do not appear to be different between hemophilia A and vWD patients treated. Because most patients received other blood products in the relevant periods of time in which the event occurred, it is difficult to ascribe causality regarding any reports of viral transmission. In the six year time period covered, there are only two cases of seroconversions (involving hepatitis C) in von Willebrand patients for which there is no record of exposure to other blood products, but for which information on other possible exposures/risk factors is limited. All other adverse reactions reported in von Willebrand patients represent the frequency and type of reactions expected from plasma derivatives.

In summary, Humate-P® is a safe product for use in patients with von Willebrand disease based on the past six year record of spontaneously reported adverse events.

Further details of the adverse experiences reported are found in Section 22(d) 12, (Volume 12, Page 001).

V. Orphan Drug Considerations

Humate-P® was granted Orphan Drug status for the indication of vWD (Ref. No. 92-679) on October 16, 1992. Centeon seeks to exercise marketing exclusivity for the vWD spontaneous and trauma-induced bleeding indication

VI. **VI. Package Insert**

A copy of the approved package insert is attached.

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