Georgetown
University
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Lombardi Cancer Center

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April 2, 2003

Dockets Management Branch
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

Re: Docket No. 02P-0435 (Citizen Petition)

To Whom It May Concern:

I am a board-certified hematologist and Director of the Hemophilia Treatment Center at Georgetown University Medical Center, a federally funded entity. Our Hemophilia Treatment Center cares for over two hundred individuals affected with von Willebrand disease from the Washington Metropolitan area and the mid-Atlantic region. As such, I am taking this opportunity to provide to you my perspective and opinions regarding the Citizen Petition, submitted to the FDA by Aventis Behring Pharmaceuticals, Inc. The Citizen Petition apparently seeks to prevent FDA approval of Alphanate for the specific indication of the treatment of bleeding events in individuals with von Willebrand disease. This is despite the fact that the only currently FDA approved plasma concentrate for treatment of von Willebrand disease does not have a surgery indication for this coagulopathy.

I wish to emphasize that I believe that both Humate P and Alphanate are excellent products and that I do not have any active contractual agreements with Alpha Therapeutic Corporation as a consultant or an employee. However, I was one of the principal investigators involved with their multi-institutional clinical trial, which investigated the safety and efficacy of Alphanate in von Willebrand disease. The data from this study are no doubt being evaluated by the FDA in their deliberations regarding the licensing of this product for use for the treatment and prophylaxis of bleeding episodes associated with and precipitated by von Willebrand disease.

The following are pertinent and compelling points, which should be considered during the FDA's deliberations for granting the von Willebrand disease treatment indication for Alphanate:

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1. Hematologists and patients remain concerned about the ability of a monopoly source of a von Willebrand factor protein-containing concentrate to maintain adequate supplies for the treatment and prophylaxis of acute bleeding complications in individuals with von Willebrand disease. Over the past several years, we have experienced shortages of therapeutic replacement concentrates for hemophilia related to various problems of quality control, donor viral and/or prion exposure, etc. This occurred in the context of multiple manufacturers (including the manufacturer of Humate-P), who were supplying plasma-based and genetically engineered products. While there appears to be an adequate supply currently of Humate-P, I remain concerned and unreassured that having only one product available for use in my patients with von Willebrand disease is prudent and adequate. Certainly if a supply issue arose involving this manufacturer, then at least there would be other options available to meet our patient's clinical needs. Furthermore, Humate-P is considerably more expensive than Alphanate. The availability of Alphanate in the marketplace would also provide us with a more cost-effective therapy than we currently have.

2. There are definite differences in the viral attenuation/inactivation processes between Alphanate and Humate-P, the only current licensed replacement concentrate available in the United States for treatment of individuals with von Willebrand disease. The dual solvent detergent and heat treatment steps for viral attenuation in Alphanate reduce the risk of transmitting nonlipid-enveloped viruses, which are resistant to solvent detergent processes and perhaps pasterization alone. The use of plasma-based concentrates in the von Willebrand disease population is worrisome to begin with since these products occasionally are administered to pregnant women. The potential risks for vertical transmission of parvovirus B19 to the fetus, which in turn could produce Hydrops Fetalis and fetal demise, cannot be ignored and the double viral inactivation process for Alphanate provides an extra theoretical and practical safeguard against this and other nonlipid-enveloped viruses. This is in contrast to the single viral attenuation step included in the purification process for Humate-P. To my knowledge, there has been no published report to indicate the rate of parvovirus B19 seroconversion in individuals receiving Humate-P.

3. Alphanate has been examined and tested extensively in a very well-controlled, large, prospective clinical trial, the results of which have been peer reviewed and published (Blood, volume 99, 2002). I am a co-author and major contributor of patients to this study and I have had the opportunity to analyze the data in great detail. This study provides the largest experience of prospective treatment of von Willebrand disease patients of all subtypes in the literature and encompassed treatment of bleeding and prophylaxis in diverse clinical situations. Prior to this study, the published medical literature contained only case reports or descriptions of vWD patient experiences with plasma concentrates in small retrospective series. Our study reported in Blood was designed to assess the efficacy of a von Willebrand factor-containing plasma-derived concentrate for the control of bleeding in both the prophylaxis and surgical scenarios. To date, Humate-P has not been studied in as extensive or methodical manner. Data confirming the efficacy of Humate-P in the surgical setting remain to be generated in a prospective clinical trial, although Aventis is planning such a trial. Completion of this

study with subsequent data analysis and scrutiny will take years. The Alphanate experience provides the physician and patients with a reliable product for surgery in von Willebrand patients; the clinical data provide reassurance that the product is efficacious and safe.

4. Humate-P and Alphanate also differ in their ratios of ristocetin cofactor activity to factor VIII:C activity. This is critically important to clinicians who do not have coagulation laboratories available to monitor von Willebrand factor activities in a timely fashion. Because dosing of Humate-P and AlphaNate on the first day of surgery is based on ristocetin cofactor units and the response of the individual patient to an infusion of either of these plasma concentrates ideally should be monitored by a von Willebrand factor assay, a product which has closer to a 1:1 ratio between ristocetin cofactor activity and factor VIII:C activity would be useful. This is the profile for Alphanate in contrast to Humate P with a much higher ristocetin cofactor activity to factor VIII:C ratio. This would enable coagulation laboratories, which do not have the ability to perform ristocetin cofactor assays, to measure factor VIII:C activity levels as an estimate of adequacy of treatment. Many laboratories do not perform the ristocetin cofactor activity assay because it is labor intensive and considerably difficult to standardize and to quality-control. This provides another theoretical advantage to making Alphanate available in the marketplace for vWD replacement therapy, particularly for surgery.

I hope that my perspective provides reasonable insights to justify the licensing of Alphanate for treatment of von Willebrand disease patients, particularly in the surgical scenario. I appreciate the fact that orphan drug status had previously been provided to Humate-P; however, the more recent clinical trials with Alphanate, the potential vulnerability of supply if one company has a monopoly on the vWD indication, the dosing issues and the dual viral inactivation processes as outline above, should provide the impetus for allowing another product into the marketplace. Physicians and patients would be very grateful to have two excellent products available.

If you have any questions or concerns, please do not hesitate to contact me.

Very sincerely,

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