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HEMOPHILIA TREATMENT CENTER
an International Hemophilia Training Center
of the World Federation of Hemophilia

Carol K. Kasper, MD
Emeritus Professor of Medicine, University of Southern California
Emeritus Vice President Medical, World Federation of Hemophilia

2400 South Flower Street
Los Angeles, CA 90007
TEL 213.742 1364
FAX 213 742 1355
E-mail: ckasper@laoh ucla edu
E-mail: carolkasper@hotmail com

March 28, 2003

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

Re: Docket # 02P-0435 (Citizen Petition)

Dear Sirs and Mesdames,

A clotting factor concentrate of factor VIII with von Willebrand factor, "Alphanate", is awaiting approval for the indication of von Willebrand disease, and I understand that Aventis-Behring has raised objections, on behalf of their competing product, "Humate-P", on grounds, if I understand correctly, of orphan drug status for the latter product.

I am strongly in favor of approval of Alphanate for the indication of von Willebrand disease, in addition to Humate-P, already licensed for that indication.

My major reason is that **supply** of the one product now licensed for use of von Willebrand disease, Humate-P, has not been adequate in recent years. Sometimes we have not been able to obtain the product, and have had to use Alphanate or Koate off-label for patients with von Willebrand disease (VWD). On one occasion, we did not have enough Humate-P in the post-surgical period for a patient with severe VWD and switched to Alphanate (which was effective). On another occasion, an entire major surgical operation on a patient with severe VWD was performed using Alphanate. I was told today, by Aventis-Behring, that the supply of Humate-P is excellent at the moment, which I hope will hold true after this contest at the FDA is settled. I am opposed to one supplier for a vital medicine, and very opposed when the product is made on another continent and (1) the needs of their local consumers may take priority and (2) disruptions in shipment are conceivable. I am old enough to remember serious wartime shortages.

A second reason is that the **safety and efficacy** profiles of Alphanate are excellent. The product is viral-inactivated with two methods, which is the standard demanded nowadays for new products. I do not agree with this demand, and believe that pasteurization alone is probably adequate. However, I have just returned from Australia, where the national regulator, the Therapeutic Goods Administration, forced the national fractionator-for-the-Red-Cross, CSL, to add a second viral inactivation step, solvent-detergent, to their heat-treated plasma-derived factor VIII concentrate, in order to meet perceived international highest standards. The solvent-detergent viral inactivation method is effective against lipid-enveloped viruses including the newly-epidemic West Nile Virus. .

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Alphanate is more highly purified from the starting plasma than Humate-P. In the 1980's, suspicions arose that less-highly-purified concentrates might contain a high proportion of proteins from the starting plasma which tended to suppress immune responses. Many doctors and patients wanted concentrates highly purified from the starting plasma. This product satisfies that perceived need. (I, myself, was not, and am not, as concerned about purification levels as the general hemophilia community.)

The efficacy of Alphanate in von Willebrand disease was studied prospectively, not only for spontaneous bleeding episodes, but also for surgical operations, in a multicenter trial led by the world's most eminent hemophilia expert, Pier M. Mannucci of Milan, Italy (in Blood 2002, 99: 450-456) and was excellent.

A third reason is a general objection to the **abuse of orphan drug laws** to bar competition among manufacturers of profitable medications. During the 1980's, Dr. Doris Menache-Aronson developed the first purified factor IX concentrate when she was working at the American Red Cross. The technology was transferred to Alpha and the final product was called "Alphanine". At licensure (1990) orphan drug status was considered but objections arose from the same rival which is objecting now, on behalf of their new purified factor IX concentrate "Mononine". The upshot was that Mononine was licensed first. I am glad that that decision spared the community from orphan drug status for a single concentrate but I hope that on this second occasion, the decision between these rivals will not again punish the same smaller company. I hope that orphan drug status will be reserved for true orphans such as congenital factor XI deficiency or other rare factor deficiencies for which we have no concentrate, and which would not be profitable to make.

I question the designation of von Willebrand disease as an orphan disease. Estimates of its prevalence generally are quoted as one in a hundred people. I believe that to be an over-estimate, but the true prevalence is not yet determined. I have heard it said that only severe VWD (type 3) patients are candidates for treatment with concentrate. Patients with other types, including the common type 1, also are candidates when having prolonged treatment, for example, for surgical operations. The alternate non-plasma-product therapy, DDAVP, is rarely given more than once a day because of its potent toxicity (water-retention) its and lack of efficacy if given more than once every one to two days. Levels of von Willebrand factor attained with DDAVP doses given every 24-48 hours may not be sufficient for surgical operations.

The situation is different from that of hemophilia, for which prevalence statistics are well-established, and which does count as an orphan.

Thank you very much for considering my opinions.

Sincerely yours,

Carol K. Kasper MD

Cc: Dr. Jesse Goodman, Director, CBER, NIH Bldg 29B, Room # 5, Bethesda, MD 20892