

Baxter

BioScience

14 May 2004

Food and Drug Administration
Center for Biologics Evaluation and Research
Woodmont Office Center, Suite 200N
Document Control Room HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Re: Response to Warning Letter, CBER-04-005 (BLA STN # 103133)
Polygam[®] S/D [Immune Globulin Intravenous (Human)]
Dated 11 May 2004
Baxter Healthcare Corporation, U.S. License 140

Attention: James S. Cohen, J.D., Acting Director
Office of Compliance and Biologics Quality (HFM-600)

Dear Mr. Cohen:

This letter is the response by Baxter Healthcare Corporation, Baxter Bioscience (Baxter) to the 11 May 2004 Warning Letter issued by the FDA concerning a professional print advertisement (2003-72) for Polygam S/D [Immune Globulin Intravenous (Human)], which Baxter had submitted to FDA on 22 January 2004 with Form FDA 2253. Baxter received the Warning Letter via facsimile on 11 May 2004, and both Baxter and the product's distributor, American Red Cross (ARC), have reviewed it carefully.

We would like to clarify that the promotional material submitted to FDA by Baxter on 22 January, 2004 and attached to your Warning Letter, does not reflect the advertisements as they were actually published. See Exhibit A for reprint of the actual advertisement, which appeared in four journals over several months. You will note that the published advertisements included warning and cautionary statements, which FDA has identified as absent in the version FDA received with the Form 2253. We regret that these statements were inadvertently omitted from the advertisement submitted for review.

We acknowledge that the discrepancy between Baxter's 22 January 2004 submission to FDA and the actual advertisement content printed in the journals illustrates a need for corrective actions in our internal procedures. However, as the advertisement that actually appeared in journals included important risk information, we do not believe that a serious public health issue has been identified nor do we believe that a legal basis for a Warning Letter exists in this case.

Information and data contained within this application which are marked as "confidential" are trade secrets or confidential business information of Baxter Healthcare Corporation and are exempt from disclosure under the Freedom of Information Act pursuant to 5 U.S.C. §552 (b) (4) and 21 CFR Part 20.

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The first paragraph of FDA's 11 May 2004 Warning Letter states that the advertisement fails to include risk information in the main part and is misleading with respect to risk information and thus does not include a true statement in brief summary as required. Furthermore, the Warning Letter states that the advertisement presents a serious public health issue, because it could encourage the unsafe use of Polygam S/D. Please note, however, that the published advertisements included warning and cautionary statements, which FDA identified as absent in the version FDA received with the Form 2253. Specifically, the published advertisement includes risk information relative to renal dysfunction, acute renal failure, osmotic nephrosis, and infectious disease. Again, this is shown in the reprint of the actual advertisement, enclosed as Exhibit A.

Further, the statement which claims that "*Polygam S/D has one of the lowest IgA content levels*" is appropriately referenced at the bottom of the advertisement in the citation by Cunningham-Rundles. The Cunningham-Rundles article reference describes the use of low IgA containing IGIV preparations (described as IgA levels between 0.4 and 2.9 µg IgA per mL in a 5% immunoglobulin solution) in patients with high titer anti-IgA antibodies. Use of these IgA depleted preparations in this patient group was generally well tolerated, however the authors did note a low (5.3%) rate of mild to moderate infusion reactions. Utilizing the Cunningham-Rundles criteria, Polygam S/D would be considered to be an IgA depleted product. Additionally, ARC product data on file which is cited in the advertisement, reveal that IgA levels are less than or equal to 1.2 µg IgA per mL of product.

We have the following specific responses to your Brief Summary Violations, Conclusion and Requested Action. FDA's citations are stated **in bold** followed by our response.

FDA STATEMENT:

The main part of the advertisement makes numerous claims of safety and effectiveness, but fails to provide any risk information. As noted, Polygam S/D is associated with numerous risks, including serious and sometimes fatal risks of renal dysfunction, acute renal failure, osmotic nephrosis, severe



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hypersensitivity reactions or anaphylaxis, and infectious disease. Information about these risks is pertinent to the safety and effectiveness of Polygam and, therefore, must appear in the main part of the advertisement along with the claims of safety and effectiveness information. 21 CFR 202.1(c)(3)(i).

BAXTER RESPONSE:

The print advertisement, entitled "Because Every IGIV Patient is Unique" has been placed in the following four journals by The American Red Cross and it has appeared in a total of seven issues.

Pharmacy Practice News: January 2004, March 2004

American Journal of Health System Pharmacists: March 2004

Journal of Allergy & Clinical Immunology: February 2004, April 2004

Infusion: March 2004, May 2004

In each printing, as shown in Exhibit A, the advertisement includes the following risk information in the main body of the text:

"POLYGAM[®] S/D is prepared from volunteer donor human plasma and therefore may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeld-Jakob disease (CJD) agent. Immune globulin intravenous (human) products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. While these reports have been associated with the use of many licensed IgIV products, those containing sucrose as a stabilizer accounted for disproportionate share of the total number. POLYGAM[®] S/D does not contain sucrose".

With respect to severe hypersensitivity reactions or anaphylaxis, the reference cited below the risk statement, Cunningham-Rundles, et. al, "Long-term use of IgA depleted intravenous immuno globulin in immunodeficient subjects with anti-IgA antibodies, **J. Clin Immunol.** 1993; 13:272-278 provides risk information as does the Warning statement in the brief summary on the reverse side of the advertisement. See Exhibit B for a copy of the Cunningham-Rundles publication.

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FDA STATEMENT:

Moreover, the advertisement states that Polygam S/D has one of the lowest IgA content levels of any IgIV product to accommodate patients with antibodies to IgA or selective IgA deficiencies. This statement is misleading because it appears in the main body and is not accompanied by the pertinent qualifying information from the PI regarding patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern. The statement is also not accompanied by the pertinent qualifying information from the PI regarding the risk of anaphylaxis in patients with antibodies to IgA or IgA deficiencies that are a component of an underlying primary immunodeficiency disease for which IGIV therapy is indicated. The advertisement is thus false and misleading with respect to product risks, in violation of 21 CFR 202.1(e)(5)(i).

BAXTER RESPONSE:

The brief summary directly referenced at the bottom of the main body of the published advertisement contains the statement reiterated below in italics. The statement is also substantiated with respect to low levels of IgA in treatment of patients with antibodies to IgA or selective IgA deficiencies by the referenced Cunningham-Rundles article cited at the bottom of the main body of the advertisement.

“Polygam S/D contains only trace amounts of IgA (≤ 2.2 microgram/ml in a 5% solution). Polygam S/D is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern. It should be given with caution to patients with antibodies to IgA or IgA deficiencies that are a component of an underlying primary immunodeficiency disease for which IGIV therapy is indicated. In such instances, a risk of anaphylaxis may exist despite the fact that Polygam S/D contains only trace amounts of IgA.”

FDA STATEMENT:

We request that you immediately cease the dissemination of promotional materials for Polygam S/D that are the same as or similar to the advertisement. Because of the significance of the violations described above,

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we request, further, that you disseminate truthful, non-misleading, and complete information to the audience(s) that received this advertisement.

BAXTER RESPONSE:

Baxter and ARC believe that the advertisements are in full compliance with FDA requirements for the reasons stated above. Nevertheless, ARC has interdicted those advertisements, which are not yet in press and has instructed its sales force to cease distribution of Polygam S/D brochures containing the material under review until this matter is fully addressed.

We also believe that a corrective communication by the ARC to receiving audience(s) is not required because there is no modification warranted to the content and form of the advertisement.

Baxter acknowledges that an administrative error in the preparation of our 22 January 2004 submission led to the FDA's concern over this advertisement. We deeply regret this error on our part and wish to assure the FDA that we intend to conduct a comprehensive review of our internal procedures to ensure that this error will not be repeated. At present, we have identified deficiencies in our internal procedures, which we believe led to the submittal of incorrect, non-representative copies of advertisements. We are in the process of revising the relevant procedures, WL-22-14017, *Review and Approval of Advertising and Promotional Materials in Regulatory Affairs*, and WL-22-14016, *First Use Advertising Submissions to FDA*. These procedures will be enhanced, reissued and implemented within 30 days. Staff will be retrained on the revised procedures and the FDA will be provided a description of all corrective and preventive actions taken in a follow up to this response letter.



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Please do not hesitate to contact me at 805-372-3070, if further information is required. Alternatively, you may contact Arlene Vidor, Vice President, Regulatory Affairs at 805-372-3040 in my absence.

Sincerely,

Linda Peters, M.S.
Vice President, Global Regulatory Affairs
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