DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

AUG 19 1998

Dear Doctor:

The Food and Drug Administration (FDA) wishes to alert you to a recent review and commentary which calls into question the medical benefit of administration of albumin or plasma protein fraction (PPF) to seriously ill patients. The relevant article, editorials and letters appeared in the July 25, 1998 issue of the British Medical Journal (BMJ 1998;317:235-240 and 317:0, 317:223, 317:240, 317:277 et seq.). This publication is available both in print form and on the Internet (http://www.bmj.com/cgi/content/full/317/7153/0, /223, etc.).

Briefly stated, a meta-analysis of virtually all existing randomized, controlled clinical studies of albumin and PPF use was performed by reviewers affiliated with the Cochrane Injuries Group, Department of Epidemiology and Public Health, Institute of Child Health, London WC1N 1EH, England. Using mortality as the endpoint, the reviewers tabulated the available data (supplementing it, when necessary, with mortality data obtained directly from the authors) and subjected the data to statistical analysis to determine relative risk of mortality by treatment. The analysis revealed excess mortality of approximately six percent (i.e., one excess death per 17 treated patients) for combined groups of patients with hypovolemia, burns, or hypoproteinemia who received albumin either instead of or in addition to crystalloid solutions. An increased mortality risk was seen also in each patient subgroup (statistically significant for patients with burns or hypoalbuminemia; borderline statistically significant for patients with hypovolemia). On the basis of their analysis, the authors concluded that albumin should not be given to critically ill patients outside of rigorously conducted, randomized, controlled trials. This conclusion also was shared in an accompanying editorial by Martin Offringa, Consultant Neonatologist, Emma Children's Hospital, Academic Medical Center, 1105 AZ Amsterdam, Netherlands, although in a follow-up letter (BMJ August 1,1998;317:343) he clarified this position as a recommendation for stringent review of albumin use. Similar conclusions were reached in a prior review (Schierhout and Roberts, BMJ March 28, 1998;316:961-964).

It is FDA's current view that the cited studies warrant serious consideration. FDA encourages additional controlled trials on the use of albumin and PPF and is committed to working with the product manufacturers to determine whether the label indications for albumin and PPF should be revised. Until the results of further, well-focused studies are available, the FDA urges treating physicians to exercise discretion in use of albumin and PPF based on their own assessment of these data. Physicians should be mindful of the importance of current treatment guidelines (for example: University Hospital Consortium guidelines for the use of albumin, nonprotein colloid, and crystalloid solutions, Arch Intern Med 1995;155:373-379), while recognizing that these guidelines themselves may require change.

Sincerely yours,

David Feigal, M.D., M.P.H.
Medical Deputy Director
Center for Biologics
Evaluation and Research