UNITED STATES PUBLIC HEALTH SERVICE
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

NIH Bldg 29
Room 323
Ph:(301) 496-2577
FAX:(301) 402-2780

Internal Memorandum

Date: 1-28-09

From: Jaroslav G. Vostal, M.D., Ph.D.
Laboratory of Cellular Hematology
Division of Hematology, HFM-335

REVIEWED
By Jaroslav G. Vostal at 6:16 pm, Jan 29, 2009

To: Salim Haddad, MD
Laboratory of Cellular Hematology
Division of Hematology, HFM-335

Subject NDA 080041, Nonclinical Pharmacology and Toxicology, InterSol Platelet Additive solution, PAS III.

Background

InterSol Platelet Additive solution, also referred to as Platelet Additive Solution III (PAS III) is a buffered solution that was developed by Fenwal to support storage of S59 pathogen reduced platelets (S59 PRP). S59 psoralen is a chemical additive of a pathogen reduction process developed by Cerus Corporation with support from Fenwal (then Baxter). The S59 pathogen reduced platelets were evaluated in a US Phase III clinical trial in the year 2001 (SPRINT trial). The pathogen reduction process includes re-suspension of platelets collected by apheresis on an AMICUS instrument in a ratio of 35% plasma and 65% PASIII, addition of the S59 to the platelets, illuminating the mixture with UV A light, incubating the illuminated mixture with an absorption device to remove un-reacted S59 and storage of the cells in the plasma additive solution mixture for up to 5 days at room temperature. PASIII alone was evaluated as apart of the pre-clinical evaluation of S59PRP in several animal studies where it served as the control vehicle. Fenwal is now proposing using PASIII as a stand alone additive solution for the storage of platelets without pathogen reduction processing.

Clinical practice and experience

Apheresis platelets stored in PASIII additive solution contain 190-245 ml of PASIII and buffy coat platelets (used in Europe) contain 190-245 ml of PASIII. Platelet products are transfused to thrombocytopenic patients over approximately an hour. Usually one apheresis platelet unit every other day or every third day based on the patient's platelet count. The infusion rate under these conditions is on the order of 4-6 ml/kg. In some cases, such as trauma, large numbers of platelet units need to be infused in a short period of time (hours). In such cases the volume of PASIII infused with the platelets could be 40-80 ml/kg.

US clinical trial of S59 pathogen reduced platelets followed 317 patients who received platelets processed and stored in PASIII and the S59 chemical. In some European countries the S59 pathogen reduced platelets have been approved and hundreds of thousands of patients have been transfused with platelets processed and stored in PASIII.

PASII is another platelet additive solution used for storage of platelets in Europe. Main difference between PASII and PASIII is the presence of Phosphate buffer in PASIII.

Composition

	PAS III g/L	PAS II g/L
Na_2HPO_4	3.05	
NaH_2PO_4	1.05	
NaCitrate Dehydrate	3.18	2.94
NaAcetate Trihydrate	4.42	4.08
NaCl	4.52	6.75
HCL		QS to pH 7.4
H_2O	QS to 100 ml	QS to 100 ml

Pre-clinical Toxicology

Study # Bio Research Laboratories	Species	Infusion rate of PASIII	Dosing interval
53779	Rat	5 ml/kg IV	28 days
53780	[redacted] dog	"	28 days
53733	Rat	"	14 days
53776	[redacted] dog	"	14 days
54477	Rat	"	7 days
53778	[redacted] dog	"	7 days
53847	[redacted] dog	80 ml/kg IV	Single dose

Pre-clinical toxicology was performed on PASIII as part of a toxicological evaluation for S59 pathogen reduced platelets. In the studies listed above PASIII and PASIII/ platelets were the controls for evaluation of S59 treated platelets in a number of animal studies that included acute and chronic administration. In all studies performed no systemic toxicity was observed and post mortem evaluation of organs revealed no toxicity issues associated with PASIII or with PASIII and platelets without S59.

Conclusion

PASIII is a crystalline solution with a composition very similar to PASII, a platelet additive solution used for preservation of human platelets in Europe. The main difference between these solutions is the presence of a phosphate based buffering solution in PASIII. Pre-clinical evaluation of PASIII in animals was done as a part of the safety evaluation of a pathogen reduction process that used P ASIII. When PASIII was infused alone or with platelets no evidence of toxicity was found at rates similar to clinical applications and also with a large bolus infusion. Based on prior clinical experience, lack of toxicity in the animal studies and low inherent toxicity of low concentration phosphate-based buffering solutions, I conclude that PASIII is nontoxic in doses anticipated in routine platelet transfusions.