



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

To: BLA STN 125389
Cross Reference: IND 13353
From: Evi Struble, Ph.D.
Through: Dorothy E. Scott, M.D.
Applicant: Biotest Pharmaceuticals Corporation
Product: Bivigam®, Immune Globulin Intravenous (Human) 10%
Subject: Final Memo, Nonclinical Pharmacology/Toxicology

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Introduction

This memo is an addendum to the PT memo signed Aug 26, 2011 which contained two CR items.

18. The amount of PS80 administered in a labeled dose of Bivigam has been associated with hepatic or renal failure (Giannattasio F, et al PubMed id:12402666; Rhodes A et al, PubMed id: 8491409). Please submit a proposal to address these concerns postmarketing. Alternatively, you may consider reducing the amount of PS80 in your final formulation.

19. Please submit a toxicological assessment on the clinical safety of glycine.

Review of the submission

The sponsor submitted the requested information and chose not change the formulation of Bivigam. The postmarketing surveillance plan will monitor for liver or kidney toxicity. This reviewer defers to the expertise of the clinical reviewers regarding the adequacy of the postmarketing surveillance plan proposed by sponsor.

Labeling

Bivigam® formulation contains a 10 times higher concentration of PS80 when compared to other IGIV products, thus carrying a risk for cardiovascular, hepatic and renal adverse events in the clinic. These effects were not seen in the clinical study performed in support of this BLA.

Animal studies that refer to these adverse effects can be noted in the appropriate section of the PI for Bivigam. Specifically, National Toxicology Program Technical Report 415, 1992 refers to “a slight blood pressure decrease” in multiple animal species, including monkeys. In rats, a bolus of Polysorbate 80 administered intraperitoneally at a dose 500 mg/kg, 25 times higher than maximum daily dose from Bivigam, resulted in an increase liver enzymes (AST, ALT, GLDH, and LDH) and total bilirubin (Pestel et al, Effect of commonly used vehicles on gastrointestinal, renal, and liver function in rats, J Pharmacol Toxicol Methods. 2006 Sep-Oct;54(2):200-14). Letter ready comments are included below.

Letter Ready Comments

1. Please include section 13 in the PI for Bivigam. An example of information that should be included in this section is shown below. These or other pertinent publications can be cited in this section: a) National Toxicology Program Technical Report 415 and b) Pestel et al, Effect of commonly used vehicles on gastrointestinal, renal, and liver function in rats, J Pharmacol Toxicol Methods. 2006 Sep-Oct;54(2):200-14.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effects of Bivigam® or its effects on fertility.

13.2 Animal Toxicology and/or Pharmacology

No animal studies were conducted to evaluate possible toxicity of Bivigam® in animals.

Bivigam contains Polysorbate 80 at a concentration of up to 2.5 mg/mL. Intravenous administrations of Polysorbate 80 in multiple species have been linked with a decrease in blood pressure. In rats, single doses of Polysorbate 80 that were up to 25 times higher than the amount from 800 mg/kg Bivigam resulted in an increase of liver enzymes and total bilirubin.