



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

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To: BLA STN 125389
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Applicant: Biotest Pharmaceuticals Corporation
Product: Bivigam®, Immune Globulin Intravenous (Human) 10%
Subject: Mid-cycle Memo, Nonclinical Pharmacology/Toxicology

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Brief Description of BLA Submission

Bivigam® is a liquid formulation of plasma derived human immune globulin (IgG). Its specifications are shown in Table 1 (adapted from Table 3.2.P.5.1-1 Specifications of Biotest-IGIV drug product). There are no animal studies submitted with this application.

Table 1 Specifications of Bivigam®

pH	4.0 – 4.6
Protein	90 – 110 g/L

------(b)(4)----- -----	------(b)(4)----- ------(b)(4)----- ------(b)(4)-----
------(b)(4)----- Purity (Protein Composition)	≥ 96%
Identity (Human)	Human – Positive
Chloride	100 – 140 mM
Glycine	200 – 290 mM
Polysorbate 80	0.15 – 0.25%
------(b)(4)-----	------(b)(4)----- ------(b)(4)-----
------(b)(4)-----	------(b)(4)-----
IGIV Potency (Polio Titer)	------(b)(4)----- ---- ------(b)(4)----- ---- ------(b)(4)-----
IGIV Potency (Measles Titer)	≥ 0.60x CBER Ref Std, Lot 176 or ≥ internal std
IGIV Potency (Diphtheria Titer)	------(b)(4)-----
------(b)(4)-----	------(b)(4)-----
Particulate Matter	------(b)(4)----- ------(b)(4)-----

Proposed indication

Primary Immune Deficiency Disorders (PIDD)

Dose

300-800 mg/kg every 3-4 weeks infused intravenously at a rate up to 350 mg/kg/hr (3.5 mL/kg/hr).

Main Findings

This BLA does not contain any animal studies performed with the preparation. Toxicological assessments for manufacturing process impurities TNBP and TritonX (report numbers be-008-91 and be-009-91 respectively) were submitted.

During the pre-BLA meeting the sponsor was made aware of the high content of Polysorbate 80 (PS80) in the formulation of the proposed product where it is used as a stabilizer. Sponsor was advised to consider possible cardiovascular effects, namely hypotension due to PS80 infusion seen in dogs and perform studies to assess the risk of similar response in humans. Report number DFP-BTT-001-V3 titled “White Paper:

Argument for the Use of Polysorbate 80 as a Major Excipient for the Biotest-IGIV Formulation” submitted with the BLA concluded that, based on data from the clinical study, hypotension was not a concern for the patient population. Notably, other IGIV preparations contain PS80 (Table 2) as an impurity following solvent detergent treatment, thus in much smaller amounts.

Table 2 Concentration of PS80 in IGIV Products and Bivigam®

Product Name/Concentration (Sponsor)	PS80 Concentration
Gammaplex/(b)(4) (BPL)	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
IgPro20/20% (CSL)	----- (b)(4) -----
Bivigam®/10% (Biotest)	----- (b)(4) -----

Glycine is another excipient used in Bivigam®. It is also used in other approved products as shown in Table 3. Bradycardia, tachycardia, hypotension, and ECG changes have been observed and correlated with systemic exposure to glycine after irrigation with 1.5% (0.21 M) glycine solution following transurethral resection of the prostate (TURP).

Table 3 Concentration of Glycine in Approved Products and Bivigam®

Product Name/Concentration (Sponsor)	Glycine Concentration
Gamunex (Talecris)	----- (b)(4) -----
Gammagard Liquid/10% (Baxter)	0.25 M
Gammagard S/D/5% (Baxter)	0.30 M
Bivigam®/10% (Biotest)	----- (b)(4) -----
Alphanate/150 IU/mL (Grifols)	----- (b)(4) -----

Conclusions

This reviewer did not identify any nonclinical issues that would prevent this BLA from being approved.

Based on the excipient profile of Bivigam®, the possibility exists for cardiovascular adverse events in the clinic. Hypersensitivity to glycine and PS80 containing products has been reported.

It is suggested that the patient population be monitored for cardiovascular effects as part of post marketing surveillance.

Questions for Sponsor

Glycine concentration in Bivigam® is higher than some other IGIV products in the market. Please submit a toxicological assessment on the clinical safety of glycine.

How is the “worse case scenario” concentration of –(b)(4)---for TNBP (report number be-008-91) and TritonX (report number be-009-91) calculated?

Analysis of Excipients and Impurities in Bivigam®

Glycine

Glycine is a non-essential amino acid present in human plasma at concentrations up to 300 µmol/L (0.3 mM) or higher (1, 2). It plays a physiologic role as neurotransmitter inhibitor in post-synaptic neurons of spinal cord, brainstem, and retina. Glycine is a required co-agonist (with glutamate) for N-methyl D-aspartic (NMDA) receptors where it plays excitatory role. However, it is reported that glycine crosses BBB at minimal amounts.

Several clinical reports have linked the use of 1.5% (0.21 M) glycine to cardiovascular disorders resulting from systemic absorption of glycine irrigation solution during genitourinary surgical procedures. Effects may include: hypotension, bradycardia, chest pain, nausea, and visual disturbances referred to as transurethral resection (TUR) syndrome (data obtained from -----(b)(4)----- database). Hypersensitivity to glycine has been reported.

The main elimination of plasma glycine may be its use in metabolism following intracellular uptake. In a study of the effects of glycine solution irrigation during urologic surgical procedures, intracellular accumulation in muscle tissue was noted at its maximum level 6 hours postoperatively (3). The same study noted the elimination half-life to be 85 minutes.

PS80

Report number: DFP-BTT-001-V3

Title: “White Paper: Argument for the Use of Polysorbate 80 as a Major Excipient for the Biotest-IGIV Formulation”

Performing Laboratories: -----(b)(4)-----

Sponsor Conclusions

- There was hypotension seen in dogs related to the infusion of PS80 at levels similar to the levels resulting from Bivigam® infusion. These effects may be species specific; the effect is not seen in non-human primates which were not sensitive to PS80.
- Clinical studies have shown no “consistent untoward changes in cardiac function, as measured by systolic and diastolic blood pressure, and heart rate.
- Taxotere (Docetaxel), an approved product indicated in several metastatic cancers, results in systemic circulating levels of PS80 (C_{max} and AUC) substantially higher than Biotest-IGIV.

Reviewer Comments and Conclusion

Maximum Daily Dose (MDD) of PS80 calculated from the dose being sought (800 mg/kg) and the maximum amount in the final product (0.25% or 2.5 mg/ml) is 20 mg/kg.

This reviewer agrees with the conclusions regarding the animal models and the likelihood that hypotensive changes seen in dogs following PS80 may be species specific.

The reviewer defers to the clinical reviewer regarding “no consistent untoward changes in cardiac function” observed in the clinical trials.

Taxotere comparison may not be appropriate due to the different patient population.

The FAO/WHO Expert Committee on Food Additives has established a maximum acceptable daily oral intake of Polysorbates of 25 mg/kg, compared to 20 mg/kg PS80 resulting from 800 mg/kg dose of Bivagam®.

PS80 may increase the absorption of fat-soluble substances. At a dose of approximately 30 times the one present in Bivagam® Polysorbate80 caused fatalities in new born babies. Low-birth-weight infants injected with α -tocopherol in polysorbate vehicle showed unexplained hypotension, thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, and metabolic acidosis. The mechanism is thought to be suppression of human lymphocytes to phytohaemagglutinin related to polysorbate-induced alteration of membrane fluidity in cells of vessel walls (4).

The same effect was observed in rats, dogs and new born rabbits. After repeated administration in rabbits at dose 2-3 g/kg/day, more than 100 times Bivagam® dose, Polysorbate 80 produces kidney damage, namely lipid accumulation in kidney cells.

Hypersensitivity due to polysorbate 80 has been reported. Anaphylactoid or hypersensitivity reactions have occurred in patients after treatment with -----(b)(4)----- and docetaxel, both containing PS80.

At oral doses up to 25 g/kg, more than 1000 times Bivagam® dose, Polysorbate80 displays equivocal evidence of carcinogenic activity in rats.

References

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2. Nathalie Lepage, Nancy McDonald, Louis Dallaire, and Marie Lambert Age-specific distribution of plasma amino acid concentrations in a healthy pediatric population, *Clin. Chem.*, Dec 1997; 43: 2397 - 2402.
3. Norlen H, Allgen LG, Vinnars E, et al: Glycine solution as an irrigating agent during transurethral prostatic resection. *Scand J Urol Nephrol* 1986; 20:19-26.
4. Golightly LK, et al. Pharmaceutical excipients: adverse effects associated with inactive ingredients in drug products. *Med Toxicol* 1988; 3: 128-65 and 209-240. (PubMed id:3287089)
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------(b)(4)-----
