Nonclinical Pharmacology/Toxicology Memo - June 25, 2009 - Gammaplex

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To: BLA STN 125329/0
Cross Reference: BB-IND--(b)(4)-
From: Evi Struble, Ph.D.
Through: Dorothy E. Scott, M.D.
CC: Kelly R Lewis and Debra Cordaro, RPM, HFM-370
Applicant: Bio Product Laboratory
Product: IGIV (Human) 5% - Gammaplex
Subject: Final Memo, Nonclinical Pharmacology/Toxicology

Brief Description of BLA Submission:
Gammaplex is a ready prepared solution of 5% human normal immunoglobulin G (IgG) from healthy US plasma donors. It is a next generation product with its predecessor, Vigam Liquid, marketed in UK since October 1997. Gammaplex differs from Vigam Liquid by ----------(b)(4)---------- step in the manufacturing process, and its formulation. Gammaplex does not contain sucrose and albumin in its formulation; two excipients are added for stability and to prevent ---(b)(4)---, sorbitol and additional amounts of polysorbate 80 (also referred here as Tween80). Due to these changes, Gammaplex is considered a new product.
Proposed indication: For replacement therapy for primary immunodeficiency disease.
Dose: Starting dose is 400-800 mg/kg maintenance dose is 200-800 mg/kg every 2-4 weeks for maintaining a trough level of at least 4 – 6 g/L at a maximum infusion rate of 0.08 mL/kg/minute. The highest dose used so far in the clinic was 799 mg/kg.
Conclusion:
From the nonclinical Pharm-Tox point of view this application can be approved. Please note the proposed label changes.
Label Review
The following are the suggested label changes for the Pharm-Tox section.

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13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, mutagenesis, impairment of fertility
[Note to sponsor: Please add appropriate information]
Suggestion:
No animal studies were conducted to evaluate the carcinogenic or mutagenic effects of Gammaplex® or its effects on fertility.
13.2 Animal Toxicology and/or Pharmacology
Gammaplex® was tested in two nonclinical studies in rats to check for hemodynamic cardiovascular side effects after intravenous infusion. Gammaplex® dose of 630 mg/kg

infused at a rate of 4.2 mL/kg/h did not cause significant changes in blood pressure and heart rate in rats. The same dose of Gammaplex® administered in rats at infusion rates in excess of 6 mL/kg/h caused an increase in blood pressure up to 20%.

Key Findings and Conclusion

The max single use dose of Gammaplex is 1g/kg. Maximal Daily Dose (MDD) for the excipients and impurities at this dose, calculated from the release specifications (Table 1) or provided by sponsor, are:

-(b)(4)- mg/kg Polysorbate 80

------(b)(4)----------

------(b)(4)-----

-(b)(4)- g/kg Sorbitol

-(b)(4)- mmol/kg or -(b)(4)- mg/kg Glycine

These excipients and impurities are present in other licensed IV products found in the PDR. For example, Alphanate contains -------(b)(4)----- and, when used as directed results in an exposure to -----(b)(4)----- mg/kg/day, similar to the exposure following Gammaplex use. Flebogamma contains sorbitol amounts that are similar to Gammaplex for similar exposure. Exposure from Polysorbate80 contained in Gammaplex is smaller that the exposure received from Nabi HB, calculated at 3 mg/kg.

Safety of the new excipients and in process contaminants is assessed via a literature search which is summarized below:

- -(b)(4)- - MDD in Gammaplex -(b)(4)- mg/kg

  NOAEL in GLP chronic studies reported from other submissions were 26 and 10 mg/kg/day for mice and rats respectively or more than 106 times Gammaplex dose.

  -(b)(4)- differs from other organophosphates because it does not inhibit brain neurotoxic esterase (NTE) in hens. After repeated oral administration, -(b)(4)- shows some neurotoxicity in mice, namely retraction of Schwann cells in unmyelinated cells of the sciatic nerve, as well as morphological changes in testes in rats at 104 times Gammaplex dose. By oral consumption it produces urinary bladder hyperplasia in rats at doses more than 103 times Gammaplex dose, also in mice at dose 180 mg/kg/day (about 104 times Gammaplex dose) and hepatocellular adenomas in male mice at doses 585 mg/kg/day.

  In conclusion, based on the data presented this reviewer judges the amount of -(b)(4)- in Gammaplex to be safe at the doses proposed.

- Polysorbate 80 – MDD in Gammaplex -(b)(4)- mg/kg

  The FAO/WHO Expert Committee on Food Additives has established a maximum acceptable daily oral intake of Polysorbates of 25 mg/kg, -(b)(4)-times the dose in Gammaplex.

  At a dose of 600 times the one present in Gammaplex Polysorbate80 caused fatalities in new born babies. 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 103 times Gammaplex dose, Polysorbate 80 produces kidney damage, namely lipid accumulation in kidney cells.

  Polysorbate80 may interfere with the antibacterial activity of fentichlor.

At oral doses up to 25 g/kg, 2x104 times Gammaplex dose, Polysorbate80 displays equivocal evidence of carcinogenic activity in rats.
In conclusion, based on the data presented, this reviewer judges the amount of Polysorbate80 in Gammaplex to be safe at the doses proposed.

- Sorbitol – MDD -(b)(4)- g/kg
  Sorbitol is listed as GRAS by the FDA.
  Rapid infusions of 15 g/kg dose in man, -(b)(4)-times the dose in Gammaplex, showed transient increase of serum concentration of uric acid and bilirubin that can be related to the liver metabolism of sorbitol.
  The safety margins for sorbitol in non GLP animal studies are small. In one study in rats a dose of 7 times Gammaplex dose is LD50, whereas another study in rats shows a dose 20 times Gamaplex dose to be safe.
  In conclusion, based on the data presented, this reviewer judges the amount of Sorbitol in Gammaplex to be safe at the doses proposed.
- --(b)(4)-- – MDD -(b)(4)- mg/kg
  Single dose toxicity studies in man and dogs at doses 120,000 and 90,000 times dose in Gammaplex respectively showed no mortalities in dogs and man. Repeated dose toxicity studies in dogs administering ---------(b)(4)---------- IV for 28 showed a reversible dose related hemoglobin and hematocrit decrease at doses up to 90,000 times dose in Gammaplex and no mortalities.
  In conclusion, based on the data presented, this reviewer judges the amount of --(b)(4)-------- in Gammaplex to be safe at the doses proposed.

Table 1. Release Specifications for Gammaplex

Test	Limits
	2.5 g5.0 g10 g
pH at 20°C	4.8 --(b)(4)-
Osmolality, mOsmol/kg	240 -600
Total Protein, g/l	-(b)(4)-
Protein Composition Gammaglobulin, %	-(b)(4)-
	------(b)(4)-----
--(b)(4)----------	----(b)(4)----
	----(b)(4)----
Sodium, mmol/L	-(b)(4)-
Chloride, mmol/L	-(b)(4)-
Glycine, mmol/L	-(b)(4)-
Acetate, mmol/L	-(b)(4)-
Sorbitol, g/L	-(b)(4)-
Polysorbate 80, ug/mL	-(b)(4)-
--(b)(4)--	-(b)(4)-
--(b)(4)----------	-(b)(4)-

Review of the original studies submitted
Study Number: 50034
Title: A Haemodynamic Monitoring Study of Two BPL Intravenous Immunoglobulin (UK Tradename Vigam) Formulations in the --(b)(4)-- Rat
Aim: To evaluate the hemodynamic effects of two BPL IVIG formulations administered IV in the conscious --(b)(4)-- rat.

Certificates of Analysis on Appendix 7, pgs 154 and 155
GLP Study
Model: --(b)(4)-- rat, N=24 male
Design: randomized, controlled study, N=8/group. Subjects were dosed via a femoral vein catheter.
Dose: 630 mg/kg, IV for 3 hours at a rate 4.2 mL/kg/h of test article (50 mg/mL) Vigam Liquid, Gammaplex or Gammaplex vehicle control.
Outcome measurements: Pressure and heart rate were recorded using a carotid artery catheter.
Results: No significant effects related to the test products during the infusions or during the 2-hr monitoring period after infusion, compared with the Gammaplex vehicle.
A mild to moderate rise in blood pressure (20% maximum increase) was observed during and after an infusion of Gammaplex at the infusion rates in excess of 6 mL/kg/h. Overall, the occurrence of hypertensive responses in rats appear to be related to the osmotic load imposed on the vasculature, a load governed by the rate of infusion.
Conclusions: Gammaplex appears to cause no significant cardiovascular effects at an infusion rate of 4.2 mL/kg/h. This rate is approximately the same as the maximal infusion rate of 4.8 mL/kg/h proposed for Gammaplex. At infusion rates 6 mL/kg/h, only marginal hypertensive responses were observed.