



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

To: BLA, BL 125596/0
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Applicant: Baxalta US Inc.
Product: Cuvitru ®, Immune Globulin Intravenous (Human) 20%
Subject: Final Memo, Nonclinical Pharmacology/Toxicology

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Brief Description and Main Findings

Cuvitru® (also referred to as SUBQ NG 20% or Gammagard liquid 20% in the preclinical studies) is a 20% IgG solution to be administered subcutaneously for PID indication. The dosage will be adjusted to maintain individual trough levels, with the volume of injection up to 60 mL/site at an infusion rate 60 mL/hr/site.

Cuvitru® has the same formulation and purification protocol as Baxter’s 10% liquid immunoglobulin product, Gammagard Liquid with the exception of (b) (4) and formulation at a higher concentration. It is formulated in glycine, and has an acidic pH (range 4.6-5.1). Some of the specifications are shown in Table 1.

Table 1. Cuvitru® Final Release Specifications

Test Parameter	Test Method (Reference)	Specification
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Appearance	Visual Inspection	The liquid preparation is clear and colorless or pale yellow or light-brown
Bacterial Endotoxins	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Glycine	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
IgA	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Octoxynol 9 (or Triton X-100)	(b) (4)	(b) (4)
pH value	(b) (4)	4.6 to 5.1 : (b) (4)
(b) (4)	(b) (4)	(b) (4)

Polysorbate 80 (or Tween 80)	(b) (4)	(b) (4)
Protein Identity	(b) (4)	(b) (4)
Purity	(b) (4)	(b) (4)
Sterility	(b) (4)	Satisfactory
Total Protein	(b) (4)	(b) (4)
Tri-(N-butyl) Phosphate (TNBP)	(b) (4)	(b) (4)

(b) (4)

NLT = not less than

NMT = not more than

(b) (4)

The preclinical studies performed with Cuvitru® were aimed at assessing the PK properties and local tolerance of this new preparation containing a higher protein concentration compared to the approved product. Additional toxicology studies were performed with Gammagard Liquid 10% and were submitted to provide support for the new, 20% preparation.

In a PK study in dogs, Cuvitru® displayed a longer Tmax, lower Cmax and comparable half-life when administered via SC route compared to Gammagard 10% administered IV. It was tolerated at the local administration site in studies performed in rabbits and (b) (4) mini pigs. There were no unexpected toxicities observed with Cuvitru® in preclinical studies.

Conclusion

Based on the nonclinical data presented, the safety profile of Cuvitru™ when used at doses and infusion rates proposed presented no preclinical concerns.

Labeling

Letter Ready Comments for Labeling

Please add Section 13 as below:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

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

13.2 Animal Toxicology and/or Pharmacology

Animal studies were conducted to evaluate possible toxicity of Cuvitru[®] in animals. [Please summarize relevant studies here.]

Complete Review

Pharmacokinetic Studies

Study 41306, 30-Day Pharmacokinetic Evaluation in Dogs of IV versus Subcutaneous Administration of 20% IVIG (b) (4)

Species: (b) (4) dogs

Aim: To compare PK properties of human IgG after a single administration either IV or SC (b) (4).

Design: n=3/sex/dose dogs received 500 mg/kg of one of three preparations: 1) Gammagard liquid IV Lot# LE12G146, 2) 20% IGSC (b) (4) or 3) 20% IGSC (b) (4).

Outcome measures: Blood samples were collected daily for 30 days to determine the PK of human IgG using (b) (4). Pharmacokinetic parameters were determined based upon plasma IgG concentrations by noncompartmental methods using (b) (4).

Results:

PK parameters are summarized in table 2. Only Columns 1 and 2 are relevant for this application. Lower C_{max}, higher T_{max} is measured after SC administration versus IV administration whereas half-life is comparable for the two routes of administration. No sex differences were observed in PK parameters for both routes of administration.

Table 2

Parameter	Group 1 10% IVIG	Group 2 20% IGSC	Group 3 20% IGSC (b) (4)
N	6	6	6
C _{max} (µg/mL)	10883.75 ± 1510.64	3333.0 ± 554.05	5389.09 ± 567.60
T _{max} (hr)	1.38 ± 0.35	70.67 ± 26.91	41.0 ± 12.39
K _e (hr ⁻¹)	0.004 ± 0.002	0.003 ± 0.001	0.003 ± 0.001
T _{1/2} (hr)	230.48 ± 83.34	250.6 ± 74.0	216.7 ± 47.3
AUC _{0-t} (µg*hr/mL)	(1.21 ± 0.24) X 10 ⁶	(0.90 ± 0.12) X 10 ⁶	(1.30 ± 0.16) X 10 ⁶
AUC _{0-∞} (µg*hr/mL)	(1.41 ± 0.33) X 10 ⁶	(1.05 ± 0.21) X 10 ⁶	(1.46 ± 0.23) x10 ⁶
Cl (mL/hr/kg)	0.38 ± 0.1	N/A	N/A
V _z (mL/kg)	115.59 ± 26.5	N/A	N/A
F (%)	100	70.8/71.4	105.5/101.4

Local tolerance studies

Study Number PV2330801, Investigation of local tolerance of SUBQ NG 20% in rabbits, GLP study

Design: n=2/sex/dose rabbits received one of three lots of SUBQ NG 20% as a bolus injection of dose 500 mg/kg into the shaved right flank. An equivalent volume of isotonic saline was injected into the left flank of each rabbit as a negative control.

Outcome measures: Behavioral observation, macroscopic evaluation of the injection sites up to termination and necropsy (24 hr), histopathological evaluation of the injection area.

Study Number PV2340801, Investigation of local tolerance of SUBQ NG 20% (b) (4) in rabbits, GLP study

Design and outcome measures were identical to the study 2330801, (b) (4)

with IGSC or saline solution.

Results for both PV2330801 and PV2340801 studies: No changes in behavior or macroscopic changes were seen. At necropsy a small amount of subcutaneous gel-like material was observed in the right flank of all animals but not left (saline treated) side. Histopathologically, these test-item-related findings consisted of a minimal to moderate, heterophilic and histiocytic subcutaneous inflammation, minimal to moderate amounts of eosinophilic amorphous material in the subcutis on the test-item treated side. The results of this study are similar to those obtained with 500 mg/kg IGI, 10% (study AU0206W01 reviewed in BLA 125402) and are thought to be related to human anti-galactose $\alpha(1, 3)$ galactose antibodies binding to galactosyl epitopes on rabbit fibroblasts. In conclusion, IGSC, 20% induced a mild to moderate SC inflammatory reaction after a single administration in rabbits that was not different than IGI 10%.

Study Number R08155, Effects (b) (4) 10% and 20% Gammagard Liquid (GGL) in (b) (4) minipigs

Aim: to determine the feasibility (b) (4) 10% and 20% Gammagard Liquid (GGL) subcutaneously and evaluate a dose response (b) (4)

Design: n=3 animals/group received Gammagard liquid 10% or IgG 20% according to table 3. All formulations were administered subcutaneously on the backs of anesthetized male pigs. Up to two different formulations were tested on each pig at a maximum volume of 110 mL per site.

Table 3

Group No.	Dose Type	Test Article			(b) (4)	Total Dose Volume (mL)
		% GGL	Vol (mL)	(b) (4)		
1	(b) (4)	10	100	(b) (4)	(b) (4)	100
2				(b) (4)	(b) (4)	
3				(b) (4)	(b) (4)	
4				(b) (4)	(b) (4)	
5			0	0		

6		20	50	(b) (4)	(b) (4)	50
7				(b) (4)	(b) (4)	
8				(b) (4)	(b) (4)	
9	Leading Edge	10	100	(b) (4)	(b) (4)	110
10		20	50	(b) (4)	(b) (4)	60
11		20	50	(b) (4)	(b) (4)	70

* 10% GGL formulations infused at 5 mL/min, and 20% GGL formulations infused at 2.5 mL/min.

Outcome measures: Injection site observations, such as erythema, edema, and skin hardening, the continuous pressure (mmHg) exerted to administer each formulation, Complete Blood Count (CBC) and IgG analysis. Animals were sacrificed 3 days post dosing and histological evaluation of the injection sites was performed.

Results: No gross abnormalities were noted of skin sections 3 days post dosing at necropsy. There was pink/redness at injection site post dosing with full recovery within 24 h. Administration of IGSC, 20% (b) (4) (~25 mL into the infusion) resulted in a distinct bleb visible approximately 10 min into dosing, also seen in GGL 10% group after 5 minutes (25 mL) administration. At approximately 2.5 min, administration of IGSC, 20% resulted in pressures that exceeded the measurable range of the equipment (> 460 mmHg) for all three pigs, versus one animal treated with IGI, 10%. No gross abnormalities were noted in skin sections taken 3 days post dosing at necropsy.

Upon histopathology, minimal to mild mixed SC leukocyte inflammation and SC edema were observed in both 10% and 20% GGL groups. In conclusion, there was no difference in local tolerance of GGL 10% and Cuvitru® when administered SC in (b) (4) minipigs.