



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

To: BLA 125822/0
From: Evi Struble, Ph.D., Research Pharmacology, PDB I, DPD, OPPT, OTP
Through: Ewa Marszal, Ph.D., Branch Chief, PDB I, DPD, OPPT, OTP
Applicant: Kedrion SpA
Product: Qivigy, Immune Globulin Intravenous (Human) 10% Solution
Subject: Pharmacology and Toxicology Review

Contents

Description	1
Nonclinical information	2
Main Findings	2
Conclusions	3
Complete Review	3
Single Dose Intravenous Toxicity and Toxicokinetic Study in the (b) (4) Rat	3
Study Design	3
Results	4
Conclusions	4
Primary Pharmacology Study	5
Formulation	6

Description

This BLA seeks approval for Qivigy, an Immune Globulin Intravenous (IGIV) 10% solution being manufactured by Kedrion SpA for the treatment of Primary Humoral Immunodeficiency (PI) in patients 18 years of age and older. Qivigy is formulated in glycine excipient with a final pH 4-4.5 (Table 1) and is intended for intravenous injection at (b) (4) to 800 mg/kg every 3 to 4 weeks.

Nonclinical information

Two nonclinical studies were performed with Qivigy, one acute toxicity study in rats and one in vitro primary pharmacology study in fresh isolated human neutrophils.

Table 1: Kedrion 10% IGIV (Qivigy) Select Final Drug Product Release Specifications

Test	Specification
Visual Appearance (clarity, color, visible particles)	Clear, colorless/ or pale yellow, essentially free of visible particles
pH	4.0-4.5
Osmolality	240 (b) (4) mOsm/kg
(b) (4)	(b) (4)
IgG Content	(b) (4)
Total Protein Content	(b) (4)
Hepatitis B Surface Antigen Antibody (HBsAg-Ab)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Sterility	Sterile
(b) (4)	(b) (4)
Bacterial Endotoxins	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
IgA	≤ 50 mg/L
(b) (4)	(b) (4)
Protein Composition (IgG purity)	≥ 96%
Haemagglutinins Anti-A	(b) (4)
Haemagglutinins Anti-B	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Sodium caprylate content	(b) (4)
Glycine	0.20-0.28 mol/L

Main Findings

1. There were no unexpected toxicities observed in the animal study. The no-observed-adverse-effect-level (NOAEL) for Qivigy was determined to be 1 g/kg, or 5 – 1.25 times higher than the human dose.
 - a. The only adverse effect seen at the higher dose (2 g/kg, or 10 – 2.5 times higher than human dose) was reversible hemolysis and increased spleen weight; both effects are expected in animal studies with human immune globulin (IG).

- The pharmacology study showed that Qivigy added to neutrophils can result in phagocytosis of pathogenic bacteria. The phagocytotic activity was comparable to the effect seen with two approved IGIV products, Privigen and Gamunex.

Conclusions

There are no issues from the pharmacology and toxicology discipline perspective to prevent approval; approval is recommended.

Complete Review

Single Dose Intravenous Toxicity and Toxicokinetic Study in the (b) (4) Rat

Study Number: 2017-0097 (Sponsor Reference Study Number: KIG10_PC_04)

Performing Laboratory: (b) (4)

Study Design

In this GLP study, (b) (4) rats (10 /sex/group) aged ~6 weeks and weighing 183-235 (males) or 198-244 (females) were randomized to receive Qivigy (lot no 40070617), concurrent control (Gamunex 10%), or negative control (0.9% sodium chloride solution) via tail vein at a dose of 1 and 2 g/kg. For each group, a subset of n=5/sex/group were euthanized on Day 2 (end of treatment) and Day 15 (end of observation), respectively. Additionally, a satellite toxicokinetic study (TK) was performed in n=6/sex/IG group and n=3 negative control group. Design of study and dose levels used are shown in Table 2 (from submission).

Table 2. Animal study design and dose levels

Test Group	Dose (g/kg)	Volume (mL/kg)	Number of Animals					
			Main Groups				TK Groups	
			Males		Females		Males	Females
			EoT ^a	EoO ^b	EoT ^a	EoO ^b		
1	0 (negative control) ^c	20	5	5	5	5	-	-
2	1	10	5	5	5	5	-	-
3	2	20	5	5	5	5	-	-
4	2 (reference item) ^d	20	5	5	5	5	-	-
5	0 (negative control) ^c	20	-	-	-	-	3	3
6	1	10	-	-	-	-	6	6
7	2	20	-	-	-	-	6	6
8	2 (reference item) ^d	20	-	-	-	-	6	6
a = End of Treatment (5 animals/sex/group) b = End of Observation (5 animals/sex/group) c = 0.9% sodium chloride solution d = Gamunex.								

Outcome measures: daily cage-site observation, weekly body weight/food consumption, hematology, coagulation, clinical chemistry on days 2 and 15, gross pathology and histopathology. A peer review histopathologic examination was performed for the high dose animals.

TK analysis was performed using a validated (b) (4). For this, 0.5 mL blood was collected in 3 animals/time point at pre-dose and 0.333 (20 minutes), 0.666 (40 minutes), 1, 2, 4, 8, 24, 72, 168, 264 and 336 hours from the start of dosing.

Results

Clinical observations noted were transient increased respiration both in control and treated animals soon after the end of dosing. No relevant effects on body weight gain or on food consumption were noted.

A dose-dependent decrease in red blood cells and related parameters was noted in animals dosed with Qivigy; the decrease in high dose females receiving Qivigy was higher than those receiving Gamunex. Recovery was observed at the end of the observation period.

Increase in total bilirubin was seen in high dose and active control animals. Recovery was seen at the end of the observation period. These changes suggest IG-mediated hemolysis. This is a common finding in animals dosed with high dose of human IG.

Statistically significant increase of spleen weight was recorded in all treated females and in high dose males at the end of the treatment period.

Mean serum pharmacokinetic parameters of Qivigy and Gamunex after single IV administration of 1 (Qivigy) and 2 (Qivigy and Gamunex) g/kg to male and female (b) (4) rats are shown in Table 3 (from submission).

Table 3: Toxicokinetic Parameters

Parameter	Unit	Qivigy 1 g/kg		Qivigy 2 g/kg	
		Males	Females	Males	Females
C ₀	mg/mL	22.9 ⁽¹⁾	26.5	46.9	42.7
T _{last}	h	336	336	336	336
AUC _{last}	mg·h/mL	1730±119 ⁽²⁾	1870±74.5 ⁽²⁾	2700 ±203 ⁽²⁾	3200 ±212 ⁽²⁾
Parameter	Unit	Gamunex 2 g/kg			
		M		F	
C ₀	mg/mL	53.4		49.6	
T _{last}	h	336		336	
AUC _{last}	mg·h/mL	2760 ±109 ⁽²⁾		3170 ±145 ⁽²⁾	
⁽¹⁾ Maximum concentration measured 0.666 h (40 minutes) post dosing.					
⁽²⁾ Standard error of the meant (SEM).					

Conclusions

Sponsor concludes that 1 g/kg is NOAEL for Qivigy. The only adverse effect seen at the high dose (2 g/kg) was reversible hemolysis and increased spleen weight; both effects are expected in animal studies with human IG. Anti-A and Anti-D specifications for the clinical lots ensure that the hemolytic activity remains low in the clinical study.

TK analysis demonstrated that administration of 1 and 2 g/kg of Qivigy to (b) (4) rats resulted in 1) higher exposure with higher dose, 2) similar exposure in male and female animals receiving the same dose, and 3) similar exposure parameters for 2 g/kg Qivigy and Gamunex.

Reviewer Conclusions: There are no toxicity concerns for Qivigy when used according to the label.

Primary Pharmacology Study

Study Number: 17-7461, Kedrion Study Code: KIG10-PC-07

Title: Quantification of Neutrophil Phagocytosis of Qivigy- opsonized (b) (4) Assay)

Performing laboratory: (b) (4)

Aim: To measure the phagocytosis of (b) (4) pathogenic bacteria mediated by Qivigy.

Study design: In this GLP compliant study, four different Qivigy batches were compared to Gamunex and Privigen, two approved 10% IG products. Phagocytosis was measured using the (b) (4) Kit from (b) (4)

Results: Phagocytic activity for (b) (4) is shown in Tables 4 and 5, respectively as the normalized signal for Qivigy and as relative activity compared to the comparative approved 10% IVIG products. These results demonstrate anti-bacterial activity of Qivigy that is comparable between batches and with other approved products.

Table 4: Phagotest Results, (b) (4)

(b) (4)	(b) (4) Neutrophils (% Total)	% difference in phagocytic activity relative to Privigen	% difference in phagocytic activity relative to Gamunex
Test Item	Mean		
Qivigy #400017	51.8	25.0	-3.1
Qivigy #400027	48.7	17.5	-8.9
Qivigy #40070617	55.6	34.2	4.1
Qivigy #40080617	54.7	32.0	2.4
Privigen	41.4		
Gamunex	53.4		

Table 5: Phagotest Results, (b) (4)

(b) (4)	(b) (4) neutrophils (% Total)	% difference in phagocytic activity relative to Privigen	% difference in phagocytic activity relative to Gamunex
Test Item Lot	mean		
Qivigy 400017	66.0	-2.4	-5.3
Qivigy 400027	67.0	-0.9	-3.8
Qivigy	69.0	2.0	-1.0

40070617			
Qivigy 40080617	69.5	2.7	-0.4
Privigen	67.6		
Gamunex	69.7		

Formulation

The final formulation of Qivigy contains sodium caprylate, a process related impurity, at a level of (b) (4). This amount is comparable to Gamunex-C, an immune globulin product approved since 2003. The submission includes a toxicological assessment that concludes sodium caprylate is safe for the proposed use. This reviewer agrees with this conclusion.

Glycine, a non-essential organic amino acid, is added as an excipient in Qivigy at a maximum level of 0.28 M (21.02 mg/mL). Glycine at similar levels is an excipient in other IgG products, including Gamunex and Gammagard Liquid. The submission includes a toxicological assessment that concludes glycine is safe for the proposed use. This reviewer agrees with this conclusion.