

1 CLINICAL PHARMACOLOGY

1.1 Mechanism of Action

CUVITRU supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. CUVITRU also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in CUVITRU have not been fully elucidated.

1.2 Pharmacodynamics

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of CUVITRU may restore abnormally low immunoglobulin G levels to the normal range.

1.3 Pharmacokinetics

Pharmacokinetic (PK) parameters of subcutaneously administered CUVITRU were evaluated in 60 subjects with primary immunodeficiency (PI) during a clinical study in North America. [See *Clinical Studies* (14)] Subjects were treated intravenously for 13 weeks with a comparator product [GAMMAGARD LIQUID, Immune Globulin (Human), 10%] and then switched to weekly subcutaneous CUVITRU infusions. Initially, subjects were treated for up to 12 to 16 weeks at a subcutaneous dose that was 145% of the intravenous dose. A comparison of the area under the curve (AUC) for subcutaneous versus intravenous infusions was performed on 15 subjects aged 12 years and older. Subsequently, all subjects were treated with this dose for 12 weeks after which the dose was individualized for all subjects using the trough IgG levels, as described below. After approximately 4 months treatment at this subcutaneous dose, a PK evaluation was conducted on all subjects.

At this dose adjustment, the geometric mean ratio of the AUC for subcutaneous CUVITRU versus intravenous administration immune globulin 10% was 109%. The peak IgG level occurred at a geometric mean of 79 hours after subcutaneous CUVITRU administration.

In part 4 of the study, pharmacokinetic parameters for CUVITRU were assessed for 60 subjects aged 2 years and older. The pharmacokinetic parameters of CUVITRU administered subcutaneously are shown in Table 8. The median peak IgG levels were lower (1809 mg/dL) during subcutaneous treatment with CUVITRU compared to IGIV 10% administration (2602 mg/dL for 3 week intervals and 2521 mg/dL for 4 week intervals), consistent with the lower weekly dose compared with the dose administered every 3 or 4 weeks intravenously. In contrast, the geometric mean trough levels were higher with CUVITRU (1474 mg/dL), compared with those when given intravenously

(1158 mg/dL for 3 week intervals and 1019 mg/dL for 4 week intervals), a result of both higher monthly dose and more frequent dosing. Weekly subcutaneous administration resulted in relatively stable steady-state serum IgG levels compared with IGIV administered at 3 to 4 week intervals. Pharmacokinetic parameters for CUVITRU did not significantly differ between age groups. The pharmacokinetic parameters of CUVITRU for the different age groups are shown in Table 9.

Parameter	Median (95% CI) N=60
AUC [g*days/L]	115 (110 to 121)
Apparent clearance [mL/kg/day]	1.86 (1.80 to 2.17)
C _{max} [mg/dL]	1809 (1745 to 2068)
C _{min} [mg/dL]	1477 (1323 to 1535)
T _{max} [hours]	10 (71 to 119)

Parameter	Age Groups				
	2 to <5 (n=1) Median (95% CI)	5 to <12 (n=10) Median (95% CI)	12 to 16 (n=5) Median (95% CI)	16 to <65 (n=37) Median (95% CI)	> 65 (n=7) Median (95% CI)
AUC [g*days/L]	106 (N/A)	110 (87 to 121)	116 (N/A)	114 (103 to 127)	139 (89 to 158)
Apparent clearance [mL/kg/day]	1.86 (N/A)	1.85 (1.31 to 2.37)	1.80 (N/A)	1.98 (1.81 to 2.23)	1.72 (0.90 to 2.36)
C _{max} [mg/dL]	1619 (N/A)	1725 (1518 to 1892)	1732 (N/A)	1940 (1778 to 2220)	2419 (1480 to 3201)
C _{min} [mg/dL]	1527 (N/A)	1351 (1130 to 1635)	1554 (N/A)	1423 (1231 to 1524)	1585 (976 to 2000)
T _{max} [hours]	70 (N/A)	164 (70 to 167)	68 (N/A)	74 (68 to 119)	119 (24 to 164)