

**Experiment Number:** K88035  
**Route:** Gavage  
**Species/Strain:** Rats/Fischer 344

**Toxicokinetics Data Summary**  
**Compound:** Primidone/ **Analyte:** Primidone  
**CAS Number:** 125-33-7

**Request Date:** 7/11/2023  
**Request Time:** 10:03:16  
**Lab:** Battelle Columbus

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**Male**

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**Treatment Group (mg/kg)**

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**30 Gavage Plasma<sup>a,c</sup>**

**80 Gavage Plasma<sup>a,d</sup>**

**130 Gavage Plasma<sup>a,e</sup>**

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Cmax (ug/mL)	14.4 ± 0.9	39.3 ± 1.2	53.4 ± 1.9
Tmax (minute)	60.9 ± 4.6	114 ± 5	131 ± 6
Half-life (minute)	42.2 ± 3.2	78.8 ± 3.1	91.1 ± 4.1
k10 (minute <sup>-1</sup> )	0.0164 ± 0.0012	0.00880 ± 0.00035	0.00761 ± 0.00034
V1 (mL/kg)	0.767 ± 0.051	0.750 ± 0.023	0.896 ± 0.032
AUCinf_pred (ug/mL/min)	2381 ± 207	12127 ± 561	19067 ± 1034

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**Female**

**Treatment Group (mg/kg)**

**30 Gavage Plasma<sup>a,f</sup>**

**80 Gavage Plasma<sup>a,g</sup>**

**130 Gavage Plasma<sup>a,h</sup>**

Cmax (ug/mL)	27.4 ± 2.6	70.7 ± 3.3	102 ± 5
Tmax (minute)	110 ± 13	152 ± 9	179 ± 10
Half-life (minute)	76.3 ± 9.3	105 ± 6	124 ± 7
k10 (minute <sup>-1</sup> )	0.00908 ± 0.00111	0.00659 ± 0.00037	0.00558 ± 0.00030
V1 (mL/kg)	0.402 ± 0.038	0.416 ± 0.019	0.467 ± 0.021
AUCinf_pred (ug/mL/min)	8213 ± 1098	29157 ± 1921	49924 ± 3159

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**Treatment Group (mg/kg)**

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**30 Gavage Plasma<sup>b,i</sup>**

**80 Gavage Plasma<sup>b,i</sup>**

**130 Gavage Plasma<sup>b,i</sup>**

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Cmax (ug/mL)	3.31	7.12	9.68
Tmax (minute)	360	540	540
AUCinf_pred (ug/mL/min)	2944	6276	10599

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**Treatment Group (mg/kg)**

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**30 Gavage Plasma<sup>b,i</sup>**

**80 Gavage Plasma<sup>b,i</sup>**

**130 Gavage Plasma<sup>b,i</sup>**

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Cmax (ug/mL)	1.02	2.28	2.74
Tmax_obs (minute)	360	540	540
AUCinf_pred (ug/mL/min)	1115	2272	3735

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## LEGEND

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### MODELING SOFTWARE PCNONLIN

### MODELING METHOD & BEST FIT MODEL

<sup>a</sup> PCNONLIN (Statistical Consultants, Inc., Lexington, KY), one one-compartment with equal first-order absorption and first-order elimination with no lag time (Model 5)

<sup>b</sup> Phenobarbital plasma concentration versus time data were not entered into the PCNONLIN program. Reported phenobarbital toxicokinetic parameters are observed values.

### EXCEPTIONS

<sup>c</sup> Observed values for C<sub>max</sub>, T<sub>max</sub>, and AUC are 12.0 ug/mL, 90 min, and 2337 ug/mL/min, respectively.

<sup>d</sup> Observed values for C<sub>max</sub>, T<sub>max</sub>, and AUC are 37.2 ug/mL, 180 min, and 11813 ug/mL/min, respectively.

<sup>e</sup> Observed values for C<sub>max</sub>, T<sub>max</sub>, and AUC are 51.8 ug/mL, 180 min, and 17881 ug/mL/min, respectively.

<sup>f</sup> Observed values for C<sub>max</sub>, T<sub>max</sub>, and AUC are 22.4 ug/mL, 180 min, and 9687 ug/mL/min, respectively.

<sup>g</sup> Observed values for C<sub>max</sub>, T<sub>max</sub>, and AUC are 67.6 ug/mL, 180 min, and 31249 ug/mL/min, respectively.

<sup>h</sup> Observed values for C<sub>max</sub>, T<sub>max</sub>, and AUC are 104 ug/mL, 180 min, and 49977 ug/mL/min, respectively.

<sup>i</sup> Reported phenobarbital toxicokinetic parameters are observed values.

### ANALYTE

Primidone

Phenobarbital

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#### TK PARAMETERS

C<sub>max</sub> = Observed or Predicted Maximum plasma (or tissue) concentration

T<sub>max\_obs</sub> = Time at which C<sub>max</sub> predicted or observed occurs

Half-life = Lambda z Half life, t<sub>1/2</sub>, the terminal elimination half-life based on non-compartmental analysis

k<sub>10</sub> = Elimination rate constant from the central compartment also k<sub>e</sub> or k<sub>elim</sub>

V<sub>1</sub> = Volume of distribution of the central compartment, includes V<sub>d</sub> and V volume of distribution, V<sub>z</sub> apparent volume of distribution NCA,  
V<sub>app</sub> apparent volume of distribution for intravenous studies

AUC<sub>inf\_pred</sub> = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

#### TK PARAMETERS PROTOCOL

##### ANALYSIS METHOD

The plasma samples were analyzed by reverse phase high performance liquid chromatography (HPLC) with UV detection at 254 nm using 4-methylprimidone as the internal standard. Samples were analyzed without dilution and the concentration then corrected during calculations when needed to correct for a starting volume of less than 200 uL. Limit of detection is approximately 0.10 ug/mL

##### TK\_GAVAGE PLASMA

Analyte: Primidone

30 mg/kg, 80 mg/kg, 130 mg/kg Male and Female

Primidone (synonym primaclone) is a congener of the barbiturate phenobarbital, widely used in epileptic seizures. Phenobarbital is a metabolite of primidone. Rats received a single gavage dose per day (30, 80, or 130 mg primidone/kg body weight). Blood was collected at 8-9 time points post-dosing with 2 rats/sex/timepoint except the earliest timepoints for 30 and 130 mg/kg which had n equals 4 due to bleed time errors. Blood was centrifuged and plasma separated and later extracted. Time courses ranged from 15 or 30 minutes to 1320 or 1800 minutes. Non-linear fitting software (PCNONLIN Statistical Consultants, Inc., Lexington, KY) was used to fit the primidone data to a one-compartment model. Individual values at a given time point were used to determine the reported toxicokinetic parameters. Reported phenobarbital toxicokinetic parameters are observed values.

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#### TK PARAMETERS PROTOCOL (cont'd)

Analyte: Phenobarbital

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